ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114301923-57-01/F Helsinki, 29 July 2015

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

For 1,2,4-trimethylbenzene, CAS No 95-63-6 (EC No 202-436-9), 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 1,2,4-trimethylbenzene, CAS No 95-63-6 (EC No 202-436-9), submitted [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex VII, Section 9.2.1.1 of the REACH Regulation concerning ready biodegradability. 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 15 January 2015, 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 5 June 2013.

On 31 October 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 2 December 2013 ECHA received comments from the Registrant on the draft decision. On 17 January 2014 the Registrant updated his registration dossier with the submission number [redacted].

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

On 15 January 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 20 February 2015 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 2 March 2015 ECHA referred the draft decision to the Member State Committee.

By 23 March 2015 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 7 April 2015 in a written procedure launched on 26 March 2015.

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)(vii), 12(1)(e), 13 and Annexes VII and XI of the REACH Regulation the Registrant shall submit the following information using one of the indicated test methods and the registered substance subject to the present decision:

Ready biodegradability (Annex VII, 9.2.1.1.; test method: Ready biodegradability – CO2 in sealed vessels (headspace test), OECD 310)
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: MITI test (I), OECD 301C)
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: Closed bottle test, OECD 301D)
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: Manometric respirometry test, OECD 301F).

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. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **05 February 2016** an update of the registration dossier containing the information required by this decision including, where relevant, an update of the Chemical Safety Report.

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 covers endpoints relating to ready biodegradability (Annex VII, 9.2.1.1 of the REACH Regulation).

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, the endpoint 'ready biodegradability' (Annex VII, 9.2.1.1.) is a standard information requirement for registration for a substance produced or imported in quantities of 1 000 tonnes or more per year.

According to column 1 of Section 9.2.1.1 of Annex VII of the REACH Regulation, a ready biodegradability study is required to fulfil the standard information requirements. Column 2 of Section 9.2.1.1 of Annex VII further states that the study does not need to be conducted if the substance is inorganic. The registrant may also seek to adapt the information requirement under general rules for adaptation laid down in Annex XI, including weight of evidence (Section 1.2) and/or Qualitative and Quantitative structure-activity relationship (QSAR) (Section 1.3).

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. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

In the present case, the technical dossier contains four non-GLP experimental studies published in peer reviewed literature or a handbook. Three of these studies are non-guideline experimental studies and one study based on the OECD 301C test guideline (TG) was assessed as unreliable (Klimisch score 4). All this information has been used as part of the Weight of Evidence (WoE) approach to assess the biodegradability of the substance. Furthermore, the QSAR (Biowin v4.1 in EPISuite 4) estimation results for the biodegradation have been reported as a supporting study in the technical dossier. The Registrant's outcome of the WoE is that the substance is "biodegradable" under the specific test conditions described in the studies used in the WoE and the substance is not regarded as persistent (P) in the PBT assessment. Vapour pressure of 300 Pa was reported for the registered substance.

ECHA considers that the information provided in the registration dossier is not appropriate to conclude whether or not the registered substance is readily biodegradable. ECHA notes that technical dossier contains three non-GLP non guideline studies performed (1) in aquifer microcosm with conditions not specified resulting 96% degradation after a 13-day incubation, (2) with set of activated sludge inoculums (adaptations not specified) resulting degradation ranging from 12.5% to 75% within 120 h and (3) with mixtures of adapted micro-organisms resulting 100% degradation in 1 day. ECHA Guidance on information requirements and chemical safety assessment, Volume 5 Chapter R7b (November 2012) specifies that the ready biodegradability should be assessed with non-adapted inoculum in stringent screening test conditions described in more detailed in the acceptable Test Guidelines listed also in the above referred ECHA Guidance. In addition, the Registrant provides results on OECD TG study on ready biodegradability (OECD 301C) assessed as not reliable, with results presented as range of degradation from 4 to 18 %, thus failing the criteria for ready biodegradability.

ECHA also considers that the QSAR Biowin v4.1 in EPISuite 4 estimation results cannot be used to adapt the present information requirement in terms of Annex XI, Section 1.3 because the results are not adequate for the purpose of classification and labelling. QSAR approaches may be used to create data on degradation properties of a substance. In general, no quantitative estimation method (QSAR) for estimating the degree of biodegradability of organic substances is yet sufficiently accurate to unequivocally predict rapid degradation. Results from such methods may be used to predict that a substance is not rapidly degradable, or be used in a Weight of Evidence approach.

After receipt of the initial draft decision , the Registrant has provided comments and updated the technical dossier with (i) improved the robust study summaries (RSS) of the studies initially used in the WoE approach, (ii) further justification for the use of QSAR and (iii) additional WoE arguments including read across adaptation.

(i) The Registrant has updated the information in the technical dossier for the studies (1), (2) and (3) discussed above. (1) and (3) contain further information on the analytical methods, oxygen conditions and used inoculum. However, ECHA considers this additional information on the analytics not to change ECHA's conclusion that these studies are not, according to the ECHA Guidance on information requirements and chemical safety assessment, Volume 5 Chapter R7b (November 2012), appropriate to fulfil the information requirement for this endpoint. More specifically, the ready biodegradability should be assessed with non-adapted inoculum in stringent screening test conditions described in more detailed in the acceptable Test Guidelines listed also in the above referred ECHA Guidance. Study (1) has been conducted in anaerobic conditions and study (3) with adapted micro-organisms. Furthermore, the Registrant indicated that no adapted inoculum was used in performing the study (2). ECHA notes that even if the Registrant provided information on the used inoculum being not adapted, high variation in the obtained non GLP study has not been explained by the Registrant. Furthermore, the used test substance concentration (500 mg/l) is considerably higher than the recommended concentration (100 mg/L) in the Test Guidelines OECD301 and OECD310 for testing the ready biodegradability. Therefore, the studies (1-3) cannot be considered valid to fulfil the requirements for ready biodegradability endpoint.

ECHA concludes that there are no reliable guideline studies in the technical dossier that could be used to conclude whether or not the substance is readily biodegradable and the technical dossier contains contradictory data on ready biodegradability. The non-GLP, non-guideline studies provided in the dossier are not adequate to fulfil the

conditions of Annex XI, Section 1.1.2, namely they are not adequate for the purpose of classification and labelling and risk assessment.

(ii) In the updated dossier the Registrant has provided further justification for the use of the QSARs (*Biowin and BioHCwin)* as a part of the WoE. The Registrant states that "*Biowin and BioHCwin is appropriate for 1, 2, 4-trimethylbenzene as this compound clearly falls within the applicability domain of the model"* and "*the results indicate that 1, 2, 4-trimethylbenzene is expected to biodegrade rapidly with a half life of 4.4 days*". ECHA notes that one of the two presented models, BIOWIN v4.1, predicts that the substance is not readily biodegradable (models BIOWIN 3 and 5). The Registrant points out that 1,2,4-trimethylbenzene was included in the training set of the BIOWIN model. ECHA however notes that on the MITI website (http://www.safe.nite.go.jp/jcheck/template.action?ano=1704&mno=3-0007&cno=95-63-6&request_locale=en), a value of 9% degradation is reported, which indicates that the substance cannot be regarded as ready biodegradable. The other model, BioHCwin, was developed for determining quantitative primary biodegradation half-lives for individual petroleum hydrocarbons. Half-lives for primary biodegradation cannot be regarded as sufficient to predict ready biodegradability and to fulfil this standard information requirement. Furthermore, the "experimental" data are not actually measured (primary degradation) half-lives, but "recommended half-lives" based on an evaluation of available biodegradation test and monitoring data. Therefore it was not possible for ECHA to verify the quality of the underlying data.

Taking into account the above, ECHA concludes that the provided QSAR estimations do not confirm the conclusion of the Registrant for rapid degradation of the registered substance.

(iii) In the update, the Registrant has added seven studies on three read-across substances to the WoE approach. For the purpose of determining whether the WoE approach applies to the present endpoint of Annex VII, 9.2.1.1 Ready biodegradability, ECHA has assessed the many-to-one read-across approach proposed. Hereby ECHA has considered the documentation and the scientific validity of the proposed read-across approach, before assessing whether the information provided for these endpoints is compliant with the information requirements. As the scope of this decision is limited to standard information requirement of Annex VII, 9.2.1.1, ECHA has also limited its assessment of the read-across approach as it relates to this endpoint only. Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*". In the technical dossier the Registrant has provided two ready biodegradation studies on o-xylene (CAS No 95-47-6), three ready biodegradation studies on p-xylene (CAS No 106-42-3) and further two studies with m-xylene (CAS No 108-38-3).

The Registrant bases the read-across for ready biodegradability on structural similarity and similar physico-chemical properties as follows: "*The inclusion of an additional methyl functional group on the benzene ring is not expected to change the biodegradation properties of the substance significantly, and this is supported by experimental observations. The similarity in structures, water solubilities and behaviours in the aquatic environment indicate that the biodegradation of the substances is likely to be similar"*. The Registrant concludes that "*although 1,2,4-trimethylbenzene cannot be considered to be readily biodegradable, it is not expected to persist in the environment.*"

ECHA considers that the read-across approach proposed by the Registrant is not supported with information on how the ready biodegradability of the registered substance can be predicted from the information of the read-across substances. Annex XI Section 1.5. of the REACH Regulation states: 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. It is a requirement of Annex XI, 1.5., that "adequate and reliable documentation of the applied method shall be provided." As a hypothesis of the many to one read-across proposed the Registrant has provided an assumption that an additional methyl group present in the registered substance (target) would not change the biodegradation property significantly. ECHA considers that the difference in biodegradability between the target and source substances is not supported with adequate and reliable documentation, as specified below.

ECHA notes that for the endpoint of ready biodegradability a read-across from dimethylbenzenes (orto-, meta-, and para-xylene) to trimethylbenzene (target) is applied. No data has been provided on structural analogues with four or more methyl groups attached to the benzene ring. ECHA hence considers that the extent of the influence (or lack of influence) of the additional methyl group in the target substance, not present in the source substances, has not been justified. With regards to documentation provided, ECHA therefore concludes the requirement of Annex XI section 1.5. of "adequate and reliable documentation of the applied method shall be provided" has not been met.

In conclusion, the proposed many-to-one read-across approach is not justified as no evidence has been provided to support the hypothesis that an additional methyl group would not significantly change the biodegradability and consequently the potential difference in biodegradability between the target and source substances has not been adequately addressed. Therefore, the read-across submitted as part of the WoE approach to fulfil the standard information requirement of Annex VII, 9.2.1.1 Ready biodegradability is not acceptable.

ECHA notes that there is no further evidence provided by the Registrant to support the WoE such as inherent biodegradation studies. Taking into account the above, ECHA considers that the WoE relying on the non-GLP, non-guideline studies on the registered substance, QSAR estimates and the read-across adaptation, none of which complies with the relevant requirements of Annex XI (as explained above), cannot be accepted to adapt the present information requirement in the weight of evidence approach. ECHA considers that the information provided on this endpoint is not adequate to conclude on ready biodegradability. The technical dossier does not either contain acceptable adaptation in accordance with Column 2 of Section 9.2.1.1 of Annex VII or Annex XI for this standard information requirement.
ECHA hence considers that the Registrant's conclusion that the registered substance "*does not meet the criteria for ready biodegradability but is considered to be biodegradable and would not be persistent in the environment*" has not been proven.

ECHA notes that the Registrant's comment relating to classification is irrelevant to the current decision.

ECHA therefore considers that the information provided on this endpoint is not adequate to conclude on ready biodegradability. The technical dossier does not either contain acceptable adaptation in accordance with Column 2 of Section 9.2.1.1 of Annex VII or Annex XI for this standard information requirement.

Regarding the test method, depending on the substance profile, the Registrant may conclude on ready biodegradability, by applying the most appropriate and suitable test guideline among those listed in the ECHA Guidance on information requirements and chemical safety assessment, Volume 5 Chapter R7b (November 2012) and in the paragraph below. The test guidelines include the description of their applicability domain.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to perform one of the following tests within the applicability domain for volatile substances with the registered substance subject to the present decision:

Ready biodegradability (Annex VII, 9.2.1.1.; test method: Ready biodegradability – CO_2 in sealed vessels (headspace test), OECD 310).
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: MITI test (I), OECD 301C).
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: Closed bottle test, OECD 301D).
or
Ready biodegradability (Annex VII, 9.2.1.1.; test method: Manometric respirometry test, OECD 301F).

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.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.