ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114303254-64-01/F Helsinki, 30 June 2015

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

For dimethyl terephthalate, CAS No 120-61-6 (EC No 204-411-8), 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 dimethyl terephthalate, CAS No 120-61-6 (EC No 204-411-8), 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 5 March 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 25 October 2013.

On 29 January 2014 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 27 February 2014 ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex VII, Section 8.3 and Annex X, Sections 8.7.2 and 8.7.3. With regard to the information requirements of Annex VII, Section 8.3 and Annex X, Section 8.7.2, the Registrant expressed agreement to ECHA's draft decision, and Section II was not amended. The compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) has been removed from this draft decision due to the legislative amendments to the REACH Regulation regarding Annex X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning the information requirement of Annex X, Section 8.7.3. On the basis of this change of scope, Section II was amended.

On 5 March 2015 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 proposal for amendment was 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)(vi) and/or (vii), 12(1)(e), 13 and Annexes VII 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. Skin sensitisation (Annex VII, 8.3.; test method: EU B.42./OECD 429 or OECD 442A or OECD 442B);

2. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route.

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 **7 July 2016**.

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.

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.

Pursuant to Articles 10(a)(vi) and/or (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 VII, VIII, IX, and X of the REACH Regulation.

1. Skin sensitisation (Annex VII, 8.3.)

"Skin sensitisation" is a standard information requirement as laid down in Annex VII, Section 8.3. of the REACH Regulation: "The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human, animal and alternative data, (2) *In vivo* testing". Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier the Registrant has provided five study records (no guideline followed) which were not performed according to Good Laboratory Practice (GLP).

Annex XI, Section 1.1.2. establishes that non-GLP or non-guideline studies may be considered to be equivalent to test methods referred to in Article 13(3) of the REACH

Regulation provided that they are 1) adequate for the purpose of classification and labelling and/or risk assessment; 2) provide adequate and reliable coverage of key parameters in the relevant recognised test method; 3) have an exposure duration that is comparable to or longer than the relevant recognised test method; 4) is supported by adequate and reliable documentation.

The studies provided by the Registrant comprised of:

- The study EKC 1971 ("drop-on method") (indicated as a key study and as reliable with restrictions) differs significantly from the Buehler test method (test method: EU B.6 / OECD 406), which is recognised by ECHA. Like the Buehler test method, the EKC 1971 test uses only epicutaneous application. However, in the Buehler test method a minimum of 20 animals should be used for treatment group and 10 animals in the control group. In the test provided, only 10 and 5 animals were used in treatment and control group, respectively. In the Buehler test method the test substance should be applied under occluded conditions. However, in the EKC 1971 test the application occurred in open application. For the dose selection the Buehler test specifies that the induction concentration should cause mild irritation and the challenge concentration should be the highest non-irritation dose. In the EKC 1971 test the concentration chosen for both induction and challenge was only [redacted]%, which seems to be very low when looking at the substance properties (the substance is not classified for skin irritation/corrosion) and the doses used in other studies provided for skin sensitisation by the Registrant. Moreover, the Registrant has not provided information as to whether the [redacted]% dose caused mild irritation or not and hence it is not possible to evaluate if proper concentrations have been used in the study.

- The study EKC 1971 ("footpad method") (indicated as a key study and as reliable with restrictions), differs significantly from the Guinea Pig Maximisation test method (GPMT, test method: EU B.6 / OECD 406), which is recognised by ECHA. Like the GPMT test, the EKC 1971 test uses intradermal induction and epicutaneous challenge exposure. However, in the GPMT it is strongly recommended that if it is not possible to conclude that the test substance is a sensitiser a total of at least 20 test animals should be used. In this test only 10 animals were used for the test group. In GPMT the test substance for challenge exposure should be applied under occluded conditions however in the EKC 1971 test the application occurred in open application. For the dose selection the GPMT specifies that the induction concentration should cause mild to moderate irritation and the challenge concentration should be the highest non-irritation dose. The doses used in the study were [redacted]% for induction and challenge. The footpad method uses intradermal injections with adjuvant (whole rabbit blood) to the footpads and the induction dose is similar to that used in the guinea pig maximisation test; however, the challenge dose seems to be low when looking at the substance properties (the substance is not classified for skin irritation/corrosion) and the doses used in other studies provided for skin sensitisation by the Registrant. No information has been provided as to whether the induction dose caused mild irritation. The results of the study was negative; only 1/10 was positive, i.e. [redacted]% which does not appear sufficient for classification. However, a direct comparison to the CLP criteria is not possible due to the non-standard guideline.

- The EKC 1958 study (indicated as supporting study and as reliable with restrictions) differs significantly from the Buehler test method, which is recognised by ECHA. Like the Buehler test, the EKC 1958 test method uses only epicutaneous application. However, in the EKC 1958, 5 instead of 20 animals were used and, therefore, the results of this study seem questionable with respect to statistical significance and reliability. There are concerns related to the proper dose selections for induction and

challenge, where for induction the dose should cause mild irritation and the challenge should be the maximum non-irritating concentration. Moreover, the Registrant has not provided information as to whether the [redacted]% dose caused mild irritation or not and hence it is not possible to evaluate if proper concentrations have been used in the study.

- The EKC 1957 study (indicated as supporting study and as reliable with restrictions) differs significantly from a Buehler test method. Like the Buehler test, the EKC 1957 test uses only epicutaneous application. However, 5 instead of 20 animals were used in the EKC 1957 test and, therefore, the results of this study seem questionable with respect to statistical significance and reliability. There are concern related to the proper dose selections for induction and challenge, where for induction the dose should cause mild irritation and the challenge should be the maximum non-irritating concentration. It is not clear from the reporting whether the induction dose caused mild irritation. In this non-GLP and non-guideline study a concentration of [redacted]% was used and 1/5 showed positive reactions; i.e. [redacted]% which would require classification if Buehler-classification criteria were followed. The Registrant stated that based on the results of this study the substance is a sensitiser. However, the Registrant did not classify the substance as sensitising.

- The [redacted] 1955 study (indicated as supporting study and as not assignable) cannot be evaluated due to the fact that the reporting of the study is very limited. The reporting lacks details e.g. about the induction and challenge exposures and there is not information if positive and negative test groups were included in the study or not. This study was performed in 10 animals with intact skin and 10 animals with abraded skin with a concentration of 50%. The results obtained were negative; however reporting is very limited and, hence, it is not possible to adequately evaluate the study.

ECHA concludes that the above-mentioned non-guideline and non-GLP studies do not provide the information required by Annex VII, Section 8.3., in particular because the key parameters foreseen to be investigated in the corresponding sensitisation test method recognised in accordance with Article 13(3) of the REACH Regulation are not adequately and reliably covered (Annex XI, Section 1.1.2. of the REACH Regulation); i.e. from the provided non-GLP and non-guideline studies it cannot be concluded that the registered substance has or has not sensitising properties.

Furthermore, while the Registrant has not explicitly claimed an adaptation of the information requirement in Annex VII 8.3, he has provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, 1.2 (weight-of-evidence). In the technical dossier, the Registrant has stated that *"the results of the five available skin sensitisation studies are not uniformly negative as two studies report a borderline response with findings in a single animal only. However the weight of evidence from these studies (in conjunction with an absence of reported cases of sensitisation in exposed workers) leads to the conclusion that DMT is not a skin sensitiser."*

ECHA considers that the individual studies and the statement provided by the Registrant are not sufficient to satisfy the information requirement of Annex VII, 8.3., and that there is not sufficient weight-of-evidence from the combined studies and reasoning to fulfil the information requirement of Annex VII, 8.3. In particular, the overall conclusion "*that DMT is not a skin sensitiser*" is not convincingly justified in view of the positive sensitisation results. Furthermore, unspecified "weight of evidence" and "absence of reported cases of sensitisation in exposed workers" are not a basis for adaptation of the information requirement according to column 2 or Annex XI. Thus the adaptation fails to meet the requirements of Annex XI, 1.2.

ECHA emphasises that if weight-of-evidence is applied, the Registrant should address all the parameters of the endpoint concerned that may give rise to a conclusion that a substance has or has not a particular dangerous property. In this specific case, the documentation and justification should therefore address all the relevant parameters of the endpoint "skin sensitisation". ECHA notes however that the presented documentation and justification does not adequately and reliably cover all the key parameters of this endpoint (see above). There is therefore a failure to provide adequate and reliable documentation, which is a requirement of Annex XI, 1.2.

ECHA concludes that the proposed adaptation fails to fulfil two requirements of Annex XI, 1.2, and therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information on skin sensitisation derived with the registered substance subject to the present decision: local lymph node assay (test method: EU B.42./OECD 429 or OECD 442A or OECD 442B).

2. Pre-natal developmental toxicity study (Annex X, 8.7.2.)

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material. However, there is no information available for a pre-natal developmental toxicity study in a second species. The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI for this standard information requirement.

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.

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rabbit as a second species to be used.

The choice of the oral route for administration is supported by the statement in the technical dossier made by the Registrant based on three toxicokinetic studies that the registered substance is rapidly and extensively absorbed following oral administration.

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: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rabbits by the oral route.

3. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also contained a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.). As these studies are not addressed in the present decision, ECHA Secretariat 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

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://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.

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