ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114300148-62-01/F Helsinki, 15 June 2015

DECISION ON TESTING PROPOSALS SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For dimethyl sebacate, CAS No 106-79-6 (EC No 203-431-4), 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 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for dimethyl sebacate, CAS No 106-79-6 (EC No 203-431-4), submitted by [redacted] (Registrant):

- Viscosity (OECD 114);
- *In vivo* mammalian erythrocyte micronucleus test (OECD 474);
- Sub-chronic toxicity study (90-day), oral route (OECD 408);
- Developmental toxicity / teratogenicity (OECD 414);
- Long-term toxicity to aquatic invertebrates (OECD 211).

This decision is based on the registration dossier 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 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 decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

On 13 June 2013, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third-party consultation for the testing proposals from 31 January 2014 until 17 March 2014. ECHA received information from a third party (see section III below).

On 7 August 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.

On 3 September 2014, ECHA received comments from the Registrant agreeing to ECHA's draft decision, while requesting for the deadline to update the dossier to be 30 months from the adoption of the decision. The ECHA Secretariat considered the Registrant's comments. 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 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. Subsequently, proposals for amendment to the draft decision were submitted.

On 20 February 2015, ECHA notified the Registrant of the proposal(s) for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal(s) 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, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

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. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Viscosity (Annex IX, Section 7.17.; test method OECD 114);
2. *In vivo* mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2; test method B.12/OECD 474);
3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats;
4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;
5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **22 June 2017** an update of the registration dossier containing the information required by this decision.

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

A. Tests required pursuant to Article 40(3)

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

1. Viscosity (Annex IX, Section 7.17.)

"Viscosity" is a standard information requirement as laid down in Annex VII, Section 7.17. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a study following the test guideline OECD 114.

ECHA considers the proposed test appropriate and testing should be performed with the registered substance.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed test using the registered substance: Viscosity of liquids (test method: OECD 114).

2. *In vivo* mammalian erythrocyte micronucleus test (Annex IX, Section 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 IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro* study performed according to OECD 487 (*in vitro* micronucleus test) with the registered substance that shows positive results with metabolic activation (evidence of inducing micronuclei in cultured human peripheral blood lymphocytes in the presence of a rat liver metabolic activation system (S-9); no induction of micronuclei when tested up to toxic concentrations in the absence of S-9). The positive results indicate that the substance is inducing chromosomal aberrations under the conditions of the tests.

Hence, the Registrant has submitted a testing proposal for an *in vivo* mammalian erythrocyte micronucleus test according to OECD 474. ECHA notes that this test is an appropriate test to investigate effects on chromosomal aberrations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment, Chapter R.7.7.1 and Figure R.7.7-1 (August 2013).

ECHA Secretariat considers the micronucleus assay test guideline OECD 474 gives the possibility to be integrated in a repeated dose study, e.g. 90-day (OECD 408) subject to the following considerations to be taken into account by the Registrant:

- The maximum tolerated dose (MTD) in the 90-day subchronic toxicity study may be lower than the MTD in a standard micronucleus assay. For instance if the chemical does not induce toxicity, the top dose allowed by the TG is 1000 mg/kg for the 90 day sub-chronic toxicity study and 2000 mg/kg for the standard micronucleus test.
- The age of the animals and the corresponding historical controls: the laboratory performing the study should have historical control data for animals at the end of the 90-day chronic toxicity study (i.e. 13 weeks older than in the standard micronucleus assay).
- An additional group of animals, i.e. positive control group, should be added to the 90-day sub-chronic toxicity study protocol to demonstrate that the induced response are compatible with those generated in the historical positive control database.

In his comment to the proposal for amendment received from a Competent Authority Member State, the Registrant stated *"The registrant agrees with the member state competent authority to perform a combined 90 day study (OECD 408) with a genotoxicity test. The registrant has initially proposed the in vivo micronucleus test (OECD 474) in the testing plan because of a positive result in the in vitro micronucleus (OECD 487), however, the registrant has a concern because no systemic effects were observed in the OECD 422 up to 1000 mg/kg/day. As a consequence, it will be difficult to have convincing evidence that the substance have reached the bone marrow (the target organ). Therefore, the registrant proposes to ECHA and the member states competent authorities to perform a comet assay with liver and intestine to be examined according to OECD 489 (instead of the initially proposed in vivo micronucleus) combined with the 3 months repeated dose toxicity study according to OECD 408 by oral route."* ECHA considers that the proposal for amendment from the Member State explicitly indicates a combination *of* a 90-day repeated dose with an *in vivo* micronucleus test only. However, as per the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, August 2014), Chapter R.7a (Section R.7.7.6.3 at page 357) , in general combinations of *in vivo* mutagenicity tests with standard repeated dose studies are encouraged, wherever possible. Moreover, ECHA considers that in the case where the Registrant performs a comet assay combined with a 90-day toxicity study, he will need to take into account the considerations referred to above and the requirements of tissue sampling time, e.g. harvest time 24 hours after the last dose, which is typical of a general toxicity study, is not appropriate for the comet assay where samples are usually collected 2 to 6 hours after the last treatment. The aim of these additional considerations is to ensure that the generated data will be acceptable to cover the data requirement to investigate the *in vivo* chromosomal aberration concern.

As a general principle ECHA Secretariat considers there are no grounds to reject the proposal by the Registrant because this combination possibility is foreseen in the OECD 474 test guideline and in ECHA guidance R.7a section R.7.7.6.3. However, the Registrant will need to take into account the considerations referred to above to ensure that the generated data will be acceptable to cover the data requirement to investigate the *in vivo* chromosomal aberration concern.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: *In vivo* mammalian erythrocyte micronucleus test (test method: OECD 474). This study can be incorporated into the OECD 408 (90-day) oral gavage study requested in Section II.3 of this decision.

Notes for the consideration of the Registrant:

Due to the nature of the substance, the Registrant is reminded that, according to paragraph 10 of the OECD 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) "If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test". Additionally, according to paragraph 48 (d) of the OECD 474, a test chemical is considered clearly negative if "Bone marrow exposure to the test substance(s) occurred". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

Regarding follow up testing, the Registrant is reminded that according to the column 2 of section 8.4 of Annex IX 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."

3. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

a) Examination of the testing proposal

A sub-chronic toxicity study (90-day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90-day) in rats via the oral route (EU B.26/OECD 408). ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

The Registrant proposed testing by the oral route. In light of the physicochemical properties of the substance (solid with melting point at ambient temperature; low vapour pressure; not classified as corrosive/irritating to the skin) and the information provided on the uses and human exposure (no uses with spray application), ECHA considers that testing by the oral route is most appropriate.

The Registrant did not specify the species to be used for testing. According to the test method EU B.26/OECD 408, the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) Consideration of the information received during third party consultation

ECHA has received third party information concerning the testing proposal during the third party consultation.

A third party has stated that "*the registered substance meets the criteria of a 'low toxicity profile' if the proposed test on genetic toxicity in vivo will be negative. Under these circumstances the results of the sub-acute part of the OECD 422 screening assay will be predictive of low toxicity in the proposed sub-chronic toxicity study. Waiving the 90-day repeated dose toxicity study in a weight-of-evidence approach may therefore rely on the 'low toxicity profile' of the substance, and in addition on data of similar chemicals from US*

EPA's Diesters Category. In this respect a sequential testing process is recommended which gives priority to the test on genetic toxicity in vivo."

ECHA acknowledges that the third party has proposed a testing strategy including a weight of evidence approach for the Registrant to consider.

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.2. Therefore, the Registrant should assess whether he can justify weight of evidence as suggested by the third party. If the adaptation can be justified, he should include the adaptation argument with all necessary documentation in the registration dossier. Such update can only be taken into consideration in the decision-making if it is submitted before the draft decision is sent to the Member State Competent Authorities pursuant to Article 51(1) of the REACH Regulation.

However, ECHA notes that the information provided by the third party is insufficient for demonstrating that the conditions of Annex XI, Section 1.2. of the REACH Regulation are met. ECHA observes that the third party has proposed a weight of evidence approach based on a database search applying certain selection criteria. The third party claims that this general weight of evidence approach can be used to predict the sub-chronic toxic properties of a substance based on observed "low toxicity" in a sub-acute (short-term repeated dose) toxicity study if the substance fulfils certain other criteria described as a "low toxicity profile". ECHA understands, however, that it is unclear whether the substance subject to this decision meets the requirements of "*low toxicity profile*" because the "*test on genetic toxicity in vivo*" has not been conducted yet. Furthermore, ECHA notes that this predictive weight of evidence approach has shortcomings that prevent its application. First of all, ECHA notes that a weight of evidence approach requires substance-specific justification and cannot be addressed with a generic weight of evidence approach which e.g. does not explain whether it is applicable to the registered substance. Secondly, the proposed approach seems to be not robust with a limited predictive power; it is based on eighteen substances with a "low toxicity profile" including two substances for which the prediction was not correct. Thirdly, ECHA notes that the proposed general weight of evidence approach is not appropriate to conclude that a substance will not have an effect in a sub-chronic toxicity study based on results of a sub-acute toxicity study. The study design of sub-acute toxicity studies and sub-chronic toxicity studies differ in relevant key parameters affecting the uncertainty and relevance of the information obtained from these studies. For example, the reduced number of animals used in a sub-acute toxicity study (5 animals per sex and dose) compared to the sub-chronic toxicity study (10 animals per sex and dose) results in a lower statistical power of the sub-acute toxicity study to detect effects. Similarly, the duration of exposure in a sub-chronic toxicity study (90 days) covers a prolonged period of the animals' lifespan as compared to the sub-acute toxicity study (28 days). As a consequence of these differences in the study protocols, a sub-chronic toxicity study (90-day) may detect effects which were not observed in a sub-acute toxicity study (28 days). Therefore, the information provided by the third party is not sufficient to adapt the standard information requirement.

The third party also referred to supporting read-across "*data of similar chemicals from US EPA's Diesters Category*". However, the third party did not explain why prediction is possible despite the structural differences between source and target substances. Furthermore, no sufficient details of the read-across studies were provided, so ECHA cannot assess whether the read-across studies are adequate; e.g. whether the result of the proposed read across does adequately and reliably cover the key parameters addressed in the test that is replaced. Therefore, the supporting read-across cannot be accepted either.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414. ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant did not specify the species to be used for testing. He did not specify the route for testing, either. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit 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 either the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed test using the registered substance: Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

Notes for consideration by the Registrant:

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

When considering the need for a testing proposal for a pre-natal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, Section 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight-of-evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that the conditions for adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for proposing to adapt the standard information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a long-term toxicity study on aquatic invertebrates (*Daphnia magna* reproduction test, EU C.20/OECD 211) with the following justification: The risk assessment showed that, using the PNEC derived based upon acute data, there is a risk for aquatic invertebrates; so, a long-term test on aquatic invertebrates is proposed to refine the PNEC value. ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5. of the REACH Regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.2, November 2012), Chapter R.7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than aquatic invertebrates.

In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC < 1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance: Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Notes for consideration by the Registrant: Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, Section 9.1.6. If the Registrant comes to the conclusion that no further investigation of effects on aquatic organisms is required, he shall update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, Section 9.1.6.

B. Deadline for submitting the required information

The Registrant, in his comments, requested that the deadline to update the dossier be 30 months from the adoption of the decision due to capacity overload of the contract research organizations and increasing testing periods. However, the Registrant did not provide any documentary evidence of these. Therefore, ECHA did not amend the deadline.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to

the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same 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 proposed tests, 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 of the same substance to agree to the tests proposed (as applicable to their tonnage level) 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 appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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