EUROPEAN CHEMICALS AGENCY

Decision Number: TPE-D-0000002468-68-05/F Helsinki, 12 November 2012

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

**For Dibutyl fumarate, CAS No 105-75-9 (EC No 203-327-9), 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 40(1) of the REACH Regulation, ECHA has examined testing proposals set out in the registration dossier for dibutyl fumarate, CAS No 105-75-9 (EC No 203-327-9) submitted by [redacted] (Registrant), submission number [redacted], for 100-1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the jointly submitted registration dossier to fulfil the information requirements set out in Annex IX:

Annex IX, 7.16: Dissociation constant OECD 112
Annex IX, 7.17: Viscosity of liquids OECD 114
Annex IX, 9.1.5: Long-term toxicity to aquatic invertebrates OECD 211
Annex IX, 9.1.6.2: Fish short-term toxicity test on embryo and sac-fry stages OECD 212

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates after 19 July 2012, 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.

The examination of the testing proposals was initiated on 30 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 16 May 2011 until 30 June 2011. In this context, the Registrant submitted a comment on the possibility to use the results of the long term fish study of bis(2-ethylhexyl)fumarate (CAS No 141-02-6, EC No 205-448-2). No information was received from third parties.

On 14 May 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 13 June 2012 the Registrant did not provide any comments on the draft decision to ECHA.

On 19 July 2012 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 to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 22 August 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

On 3 September 2012 ECHA referred the draft decision to the Member State Committee.

ECHA reviewed the proposals for amendment received and amended the draft decision.

The Registrant did not provide any comments on the proposed amendments.

A unanimous agreement of the Member State Committee on the draft decision was reached on 8 October 2012 in a written procedure launched on 26 September 2012 and ECHA took the decision pursuant to Article 51(6) 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 requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following tests using the indicated test method:

1. Dissociation constant (Annex IX, 7.16., OECD Guideline 112 (Dissociation Constants in Water));
2. Viscosity (Annex IX, 7.17, OECD Guideline 114 (Viscosity of Liquids));
3. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant shall carry out the following tests using the indicated test method:

4. Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210);

while the originally proposed test OECD Guideline 212 for provision of Annex IX, 9.1.6; is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

Before conducting any of the tests mentioned above in points 3 and 4 the Registrant shall

consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **12 November 2013** an update of the registration dossier containing the information required by this decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance.

**1. Dissociation constant**

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

The proposed test referred to in Section II above is part of the standard information requirements as laid down in Annex IX, 7.16., of the REACH Regulation. As the dossier does not contain any information on the dissociation constant of the substance, there is a data gap for this endpoint which must be filled by data from a valid test.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus requested to carry out the following test: Dissociation constant in water (Annex IX, 7.16., OECD Guideline 112).

**2. Viscosity**

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

The proposed test referred to in Section II above is part of the standard information requirements as laid down in Annex IX, 7.17., of the REACH Regulation. As the dossier does not contain any information on the viscosity of the substance, there is a data gap for this endpoint which must be filled by data from a valid test.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus requested to carry out the following test: Viscosity of Liquids (Annex IX, 7.17., OECD Guideline 114).

**3. Long-term toxicity testing to aquatic invertebrates**

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

According to Section 9.1.5 of Annex IX of the REACH Regulation, long-term toxicity testing on aquatic invertebrates is required to fulfil the standard information requirements. 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 generate the data for this endpoint.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus requested to carry out the following test: Long-term toxicity to aquatic invertebrates (Annex IX, 9.1.5., OECD Guideline 211 (Daphnia magna Reproduction Test)).

ECHA reminds the Registrant that *"prior to testing, further guidance on testing strategies should be consulted in addition to this Annex"*, as laid down in introductory paragraph of Annexes VII-X of the REACH Regulation. Therefore, prior to conducting this test or the Fish, Early-life Stage Toxicity Test referred to in point 4) below, the Registrant shall consult the Guidance on information requirements and chemical safety assessment, Chapter R7b, Section R.7.8.5. Especially, the Registrant is requested to consider their testing strategy by taking into account the guidance (Figure R.7.8-4, p.53) related to the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on vertebrate animals. As laid down in Annex VI of the REACH Regulation, *"New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted"*.

**4. Long-term toxicity testing on fish**

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may take a decision rejecting a testing proposal in accordance with Article 40(3)(d) but requiring the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

According to column 1, Section 9.1.6 of Annex IX of the REACH Regulation, long-term toxicity testing on fish is required to fulfil the standard information requirements. 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 generate the data for this endpoint.

ECHA notes that the Registrant has not provided any justification for the testing proposal either in the technical dossier or in the chemical safety report.
According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, 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. 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 an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

The Registrant proposes to perform the test according to OECD Guideline 212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages) to cover the endpoint long-term toxicity testing on fish, Annex IX, 9.1.6 of the REACH Regulation.

However, the OECD 212 guideline does not appear to be the appropriate test to perform in order to fulfil the requirements of this end-point. Indeed, this guideline clearly states that: *'It should be borne in mind that only tests incorporating all stages of the life-cycle of fish are generally liable to give an accurate estimate of the chronic toxicity of chemicals to fish, and that any reduced exposure with respect to life stages may reduce the sensitivity and*

*thus underestimate the chronic toxicity. It is therefore expected that the embryo and sac-fry test would be less sensitive than the Full Early Life Stage test (Guideline 210), particularly with respect to chemicals with high lipophilicity (Log Kow > 4) and chemicals with a specific mode of toxic action.'*

In the present case it appears that Dibutyl fumarate has a Log Kow of 4.5. Pursuant to the guideline quoted above *Full Early Life Stage test (Guideline 210)* is more appropriate than OECD 212 for testing substances with a Log Kow > 4.

Moreover, both the ECHA Guidance on the Application of the CLP Criteria (page 459) and the ECHA Guidance on information requirements and chemical safety assessment (endpoint specific guidance in Chapter R.7b, pages 25 and 50) clearly favour the use of the OECD guideline 210 (Fish, Early-life Stage Toxicity Test) for classification and labelling and risk assessment purposes, indicating the study as the most appropriate test for substances with Log Kow above 4.

ECHA notes that in the context of the third party consultation the Registrant commented that it would be possible to use the results of the long term fish study of bis(2-ethylhexyl)fumarate (CAS 141-02-6, EC number 205-448-2) for read across.

ECHA examined the comment submitted by the Registrant and notes that no scientifically valid justification or documentation have been provided in order to support the proposed read across in accordance with REACH, Annex XI, 1.5. Annex IX, second introductory paragraph, requires the Registrant to clearly state reasons for adapting the standard information requirements according to the rules in Annex XI. In addition, the ECHA Guidance, R.6 *QSARs and grouping of chemicals* provides guidance on the issues that should be addressed in establishing a justification for a read-across. ECHA considers that the information provided to justify the read-across is insufficient to show that the aquatic toxicity effects of the registered substance may be predicted from data for the reference substance, as required by Annex XI, 1.5. As insufficient justification was provided for read-across, and the requirements of Annex XI, Section 1.5 in conjunction with Annex IX, second introductory paragraph, of the REACH Regulation are not met, ECHA cannot, at this stage, approve the validity of the read-across.

Therefore, ECHA concludes that the comment submitted by the Registrant cannot constitute a basis to reject the testing proposal on long term toxicity testing on fish.

For these reasons, pursuant to Article 40(3)(c) the Registrant is requested to carry out the following test: Long-term toxicity testing on fish (Annex IX, 9.1.6., OECD Guideline 210 (Fish, Early-life Stage Toxicity Test)). The originally proposed test OECD Guideline 212 for provision of Annex IX, 9.1.6; is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

The process of evaluation 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 evaluation 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 registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

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 European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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://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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