EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001780-77-05/F Helsinki, 13 June 2012

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

For Bis(2-ethylhexyl) fumarate, CAS No 141-02-6 (EC No 205-448-2), 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 Bis(2-ethylhexyl) fumarate, CAS No 141-02-6 (EC No 205-448-2), submitted by [redacted] (Registrant), latest submission number [redacted], for 1000 tonnes or more per year.

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

- Annex IX, 8.6.2: Sub-chronic toxicity study (90-day) according to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents). In the commenting phase the Registrant suggested to change the proposal to an OECD 422 study (extended to 90-days), to be able to combine potential chronic toxicity effects and potential reproduction toxicity effects by one study;
- Annex IX, 9.1.6: Long-term toxicity testing on fish according to OECD Guideline 212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages);
- Annex IX, 9.3.2: Bioaccumulation in aquatic species, preferably fish according to OECD Guideline 305D (Bioaccumulation: Static Fish Test); and
- Annex X, 9.5.1: Long-term toxicity to sediment organisms according to EPA OPPTS 850.1790 (Chironomid Sediment Toxicity Test).

The examination of the testing proposals was initiated on 4 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 14 February 2011 until 31 March 2011. ECHA received the following comments from third parties:

- Comments concerning sub-chronic toxicity: human data available, results of 28-day and other repeated dose toxicity studies, exposure considerations;
- Comments concerning long-term fish toxicity: degradation of substance, presence of QSAR models, use of Fish Embryo Test; and

- Comments concerning bioaccumulation: presence of valid QSAR models, other available data (invertebrate tests, field monitoring, mammalian studies).

More information is provided in the statement of reasons section below.

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40 of REACH.

On 1 September 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 27 September 2011 the Registrant provided to ECHA comments on the draft decision.

ECHA took into account the information received and decided to amend the draft decision.

On 4 November 2011 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. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 8 December 2011 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 within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided to modify the draft decision.

On 19 December 2011, the draft decision was referred to the Member State Committee.

On 20 December 2011 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 6-10 February 2012, the Member State Committee further modified the draft decision and a unanimous agreement of the Member State Committee on the draft decision was reached on 9 February 2012.

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 with the registered substance following the test using the indicated test method:

> Annex IX, 8.6.2: Sub-chronic toxicity study (90-day) according to EU test method B.26/ OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents), oral, in rat. It is at the Registrant's discretion to perform the intended additional examinations during the testing programme.

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

- Annex IX, 9.1.6: Long-term toxicity testing on fish according to OECD Guideline 210 (Fish, Early-life Stage Toxicity Test);
- Annex IX, 9.3.2: Bioaccumulation in aquatic species according to draft OECD Guideline 305 (Bioaccumulation in Fish: Aqueous and Dietary Exposure test); and
- Annex X, 9.5.1: Long-term toxicity to sediment organisms according to OECD Guideline 218 (Sediment-Water Chironomid Toxicity Test Using Spiked Sediment);

while the originally proposed tests OECD Guideline 305D for provision of Annex IX, 9.3.2; OECD Guideline 212 for provision of Annex IX, 9.1.6; and EPA OPPTS 850.1790 for provision of Annex X, 9.5.1 are rejected in accordance with Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **13 December 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 proposals of 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 take a decision requiring the Registrant to carry out the proposed test. Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may take a decision rejecting a testing proposal 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 and XI.

Examination of the testing proposals

a) Sub-chronic toxicity

According to Section 8.6.2 of Annex IX of the REACH Regulation, a sub-chronic toxicity study (90-day) is required to fulfil the standard information requirements. As the proposed test for sub-chronic toxicity is not available for the registered substance but needs to be present in the technical dossier to meet the information requirement of Section 8.6.2 of Annex IX of the REACH Regulation, it is necessary to generate the data and to perform the test.

In response to ECHA's draft decision, the Registrant proposed to perform *an extended OECD 422 study (90-day), to be able to combine picking up potential chronic toxicity effects and potential reproduction toxicity effects (fertility and teratogenicity). By performing the extended OECD 422 (90-day) the required data for 8.6.2 and 8.7.1 could be generated performing one single test, and therefore limiting the amount of animals*, according to the Registrant.

ECHA notes that it is at the Registrant's discretion to perform the modified test design and use the results to ensure the safe use of the substance. It is the responsibility of the Registrant to provide additional evidence on the compatibility of the two protocols, especially concerning histopathology in all animals, dosing issues and relative sensitivity of pregnant and non-pregnant animals. In case of modifications, Annex XI, 1.1.2. conditions

need to be met. The Registrant is also reminded that the proposed test does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, 8.7.3. unless Annex X, 8.7. column 2 adaptation is applied.

b) Long-term toxicity testing on fish

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 which is not available in the registration dossier but needs to be present being part of the standard information requirement for a substance that is registered at 100 tonnes or more per year such as the registered substance. However, the OECD 212 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.*' Bis(2-ethylhexyl) fumarate has a Log Kow of 7.9 and a Log Koc of 5.9 and therefore the less sensitive Embryo and Sac-fry test cannot be accepted.

Furthermore, both the Guidance on the Application of the CLP Criteria (page 459) and the REACH Guidance (R.7b, pages 25 and 50) clearly favour the use of the OECD 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. For these reasons, the Registrant is requested to perform the study according to OECD 210 (Fish, Early-life Stage Toxicity Test).

The Registrant responded to the ECHA draft decision on this endpoint by agreeing to this information request.

As laid down in the introductory paragraphs of Annexes VII to X of the REACH Regulation the Registrant should consult further guidance on testing strategies. Therefore, prior to conducting the long-term toxicity test on fish mentioned above, the Registrant shall consult the Guidance on information requirements and chemical safety assessment (Version 1.1, May 2008, Chapter R7b, Section R.7.8.5, page 31). More explicitly, the Registrant is requested to re-consider the testing strategy by taking into account the sequence in which the aquatic long-term toxicity tests are to be conducted according to figure R.7.8-4, p.53 of the Guidance document and the overall necessity to conduct long-term toxicity testing on vertebrate animals.

c) Bioaccumulation in aquatic species

The Registrant proposes to perform the test according to OECD Guideline 305D (Bioaccumulation: Static Fish Test) to cover the endpoint Bioaccumulation in aquatic species, Annex IX, 9.3.2 of the REACH Regulation which is not available in the registration dossier but needs to be present being part of the standard information requirement for a substance that is registered at 100 tonnes or more per year such as the registered substance. ECHA notes that the set of tests OECD 305 A to E was replaced by the OECD Guideline 305 (Bioconcentration: Flow-through Fish Test) in 1996. Therefore, the test method proposed by the Registrant is outdated and no longer suitable for chemicals of high octanol-water partition coefficient such as the registered substance.

The Registrant shall perform the bioaccumulation testing in fish following the draft OECD 305 Guideline: Aqueous and Dietary Exposure test (date of draft guideline 305: 1 December 2011; available at http://www.oecd.org/dataoecd/11/5/49190738.pdf and referred to in the REACH Guidance on information requirements and chemical safety assessment Chapter R.7.10.3.1). The draft Guideline incorporates the Fish Dietary Accumulation test, which the Existing Substances Regulation Persistent, Bioaccumulative and Toxic (PBT) working group considered appropriate under the previous chemical legislative framework and also provides additional information for selecting the most adequate exposure route. The REACH Guidance recommends the Fish Dietary Accumulation test for certain types of substances due to their specific physical chemical properties (e.g. low water solubility, high Log Kow value). For substances with Log Kow >6, such as the registered substance (Log Kow = 7.9), a dietary study as a replacement to estimate bioaccumulation is recommended. The REACH Guidance as well as the current OECD Guideline 305 (adopted in June 1996) itself also state that the Bioconcentration: Flow-through Fish Test study is most validly applied to substances with Log Kow values between 1.5 and 6.

In response to ECHA's draft decision, the Registrant commented that the registered substance would tend to float, not sink and accumulate in the sediment or on aquatic plants. Therefore, exposure by food would not be the obvious route for fish. With reference to the revised text of the draft OECD 305 Guideline currently under adoption, in particular Annex 7 'Guideline techniques for food-spiking', ECHA does not share the Registrant's view and also directs to various food-spiking techniques which can be used depending on the physical characteristics and solubility of the substance in order to promote homogeneity and facilitate good assimilation of the spiked feed.

According to the draft OECD 305 test Guideline (Bioaccumulation in Fish: Aqueous and Dietary Exposure) "*for substances that have a high log K_{OW} but still show appreciable water solubility with respect to the sensitivity of available analytical techniques, an aqueous exposure test should be considered in the first instance. But it is possible that information on water solubility is not definitive for these hydrophobic types of chemicals, so the possibility of preparing stable, measurable dissolved aqueous concentrations (stable emulsions are not allowed) applicable for an aqueous exposure study should be investigated before a decision is made on which test method to use*". The Registrant shall consider this when the test design is decided, especially as there is some remaining uncertainty in water solubility and octanol-water partition coefficient of the registered substance. It is noted that a water solubility of 1.19 mg/L would normally not be expected for a substance with a Log K_{OW} of 7.9.

If the Registrant, taking into account the above considerations, decides that the dietary exposure route is the most relevant, the approach to deriving a bioconcentration factor from this study should follow the recommendations given at Annex 8 of the draft OECD Guideline 305 (Bioaccumulation in Fish: Aqueous and Dietary Exposure).

d) Long-term toxicity to sediment organisms

The Registrant proposes to perform the test according to EPA OPPTS 850.1790 (Chironomid Sediment Toxicity Test) to cover the endpoint long-term toxicity to sediment organisms, Annex X, 9.5.1 of the REACH Regulation. This study is not available in the registration dossier but needs to be present being part of the standard information requirement for a substance that is registered at 1000 tonnes or more per year such as the registered substance. The Registrant does not justify the selection of the US national protocol

proposed and the deviation of the proposal with Article 13(3) providing that test to generate new information on 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 ECHA as appropriate. The proposed test protocol cannot be regarded as an international standard being of national origin only. Moreover, the protocol is not recognised as being equivalent to the internationally accepted OECD test guidelines. The Registrant is requested to perform the study according to OECD 218 (Sediment-Water Chironomid Toxicity Test Using Spiked Sediment).

The Registrant responded to the ECHA draft decision on this endpoint by agreeing to this information request.

Consideration of information received during public consultation

ECHA has further examined the scientific information submitted by third parties following the public consultation in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoints. This information does not, however, change the conclusion that vertebrate animal test studies need to be requested, as explained below.

a) Comments concerning sub-chronic toxicity: The third party refers to human data on systemic toxicity from repeated exposure. However, no such data was provided from the third party or the Registrant for any of the human health endpoints. The same is the case for a 28-day as well as other repeated dose toxicity studies that the third party refers to.

The third party has also proposed that the Threshold of Toxicological Concern (TTC) approach should be applied. However, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation nor has he performed an exposure assessment. Therefore, it can not be assessed if exposure is negligible.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study using the specific rules under column 2 of Annex IX, 8.6.2 of the REACH Regulation.

b) Comments concerning long-term fish toxicity: A general comment on the omission of the long-term study based on the degradation of the substance is provided. ECHA notes that biodegradation is not an Annex IX column 2 specific rule for adaptation. Furthermore, the physical chemical data (water solubility, Henry's Law constant and Log Kow) indicate that fish can be chronically exposed to the substance. Moreover, the QSAR models proposed by the third party cannot be used for waiving this information requirement due to the limited test dataset (one experimental data point) for deriving the regression line, and due to the fact that the maximum Log Kow for the model (8) is very close to the one of the registered substance. Finally, the third party indicates a new OECD guideline [Fish Embryo Test (FET)] which is not a chronic test and is still not adopted as a guideline, therefore it cannot be taken into consideration.

c) Comment concerning bioaccumulation: The third party proposes the use of QSAR models that predict a BCF of 1300-4000, without any information on the applicability domain of the model for highly lipophilic substances. The criterion of Annex XI, 1.3 to the REACH stating that the substance falls within the applicability domain of the model is not fulfilled, whilst the adequacy of the provided information for risk assessment and classification and labelling

purposes has not been established. The third party proposes caution when using the OECD 305 for very lipophilic substances. Finally, the proposal to use combined data from QSARs models with other existing data (e.g. invertebrate tests, field monitoring studies, mammalian studies, *in vitro* tests) is a general comment, whilst no such relevant information is available in the technical dossier.

In conclusion, the third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, according to Article 40(2) of the REACH Regulation, third parties are invited to submit scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal. As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis for not performing the vertebrate animal tests suggested in the current dossier.

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 generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in your dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. You 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 the joint registrants of the same substance to agree with the tests proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant. Finally, the studies must be shared by the joint registrants concerned.

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

ECHA always 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). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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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