EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114319339-46-01/F Helsinki, 17 February 2016

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

For Ethylene bis[3,3-bis(3-tert-butyl-4-hydroxyphenyl)butyrate], EC No 251-073-2 (CAS No 32509-66-3), 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 proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for Ethylene bis[3,3-bis(3-tert-butyl-4-hydroxyphenyl)butyrate], CAS No 32509-66-3 (EC No 251-073-2), submitted by [redacted] (Registrant).

- Pre-natal developmental toxicity study (OECD guideline 414) with a proposal for inclusion of additional satellite groups:
  - dosing during gestation until weaning (general examination of potential developmental effects);
  - dosing during gestation only, no dosing during lactation (examination of potential in utero effects exclusively);
  - no dosing during gestation, dosing during lactation (examination of potential developmental effects via milk).

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 submitted after the deadline for updating (14 March 2015) communicated to the Registrant by ECHA on 5 February 2015.

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

ECHA held a third party consultation for the testing proposal from 31 January 2014 until 18 March 2014. ECHA did not receive information from third parties.

On 6 June 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 11 July 2014 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of Reasons (Section III). In section II only the deadline was amended.

On 29 October 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, a proposal for amendment to the draft decision was submitted.

On 04 December 2015 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and amended the draft decision.

On 14 December 2015 ECHA referred the draft decision to the Member State Committee.

By 4 January 2016 the Registrant did not provide any comments on the proposal for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 18 January 2016 in a written procedure launched on 8 January 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following modified test pursuant to Article 40(3)(b) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414), without the proposed inclusion of additional satellite groups.

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 **24 August 2017** an update of the registration dossier containing the information required by this decision.

III. Statement of reasons

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

1. Pre-natal developmental toxicity study

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

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, in its standard design as described in the test method EU B.35/OECD 414, 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. 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 the rat or the rabbit as a first species to be used.

ECHA notes that the Registrant proposed to include 3 satellite groups in the test (for further details see Section I). The Registrant provided the following justification for this deviation from the standard study design described in the EU B.31/OECD 414 test method in section 5.9.3 of the Chemical Safety Report (CSR): "*the performance of a new developmental study with extended study design (included satellite groups in order to investigate pre- and post natal changes in development and the mode of action) to clarify the effect observed in high dose pups of a second invalid reproductive toxicity study is proposed*".

The "*second invalid reproductive toxicity study*" that the Registrant refers to was designed as a combination of a screening study for developmental and reproductive toxicity test and of a sub-chronic study. The Registrant assigned a Klimisch score of 4 to this study due to "*very restricted reporting*" and the absence of individual data. A decrease in body weight and an increase in mortality during lactation were observed among the pups of the high dose group, i.e. 800mg/kg/day. A slight growth depression of the male parent is reported for the mid and high dose groups. The Registrant indicates in the endpoint study record in IUCLID section 7.8.2 that "*the finding of decreased body weight of the pups already at day 10 suggests, that this effect does not result directly from ingestion of the test substance with the diet, but rather from change induced already during intra uterine life*". The Registrant further hypothesises that "*Taking into account the log Pow of 13.66 and the high lipophilic properties of the test substance an increased uptake of DTB glycolester via milk during the lactation phase is also thinkable*".

The Registrant proposed deviations from the standard test design and proposed to add 3 satellite groups to the test protocol in order to address the concern that he believes to have identified.

The proposed deviations from the standard test method are not accepted by ECHA for the following reason:

ECHA points out that the Registrant did not sufficiently characterise the concern. ECHA notes that the Registrant hypothesised that the effects may be due to pre-natal exposure or to exposure via lactation. However, additional information on the nature of the concern triggering the proposal for further investigations would be required for ECHA to assess the adequacy and the relevance of the proposed deviations.

While the inclusion of the satellite groups is not accepted for the above reason, ECHA also highlights that the Registrant failed to provide detailed information on the study design for each of these satellite groups. Such information relates, for instance, to the test doses planned to be used, the number of animals to be included in each satellite group, the examinations intended to be performed in each of the animals.

In the absence of more information on the potential underlying concern triggering the proposal for further investigations and without essential detailed information on the study design for each of the satellite groups, ECHA cannot assess whether the proposed deviations from the standard test design of the test method EU B.35/OECD 414 are suitable to further investigate such concern.

In its comments to the draft decision the Registrant requested an extension of the deadline to provide the requested information and provided clarifications on the nature of the concern leading to the proposal for inclusion of satellite groups to the proposed study. ECHA has accepted the request for extension of the deadline and therefore modified the deadline in section II of this decision.

According to the information provided in the technical dossier and in their comments to the draft decision, ECHA understands that the Registrant has identified a concern relating to reproductive toxicity and specifically on the potential of the registered substance to cause peri- or post-natal effects to the offpsring in a combined reproductive toxicity screening/16 weeks oral toxicity study (Study reports [redacted]). The Registrant proposes to perform a pre-natal developmental toxicity in order to fulfil the information requirement of Annex IX, 8.7.2 and to conduct additional testing in the context of this study to confirm the findings giving rise to the concern for peri- or post-natal reproductive toxicity and to further investigate the mechanism of action leading to the occurrence of the putative peri- or post-natal toxicity to the offspring. The Registrant hypothesises in the technical dossier and in his comments that the effects observed in the offspring may be "*changes induced already during intra uterine life*" or that the effects "*originated from increased uptake of the test item via milk during the lactation phase due to its high lipophilic properties as indicated by the log Pow of 13.66*".

A pre-natal developmental toxicity study is required to fulfil the information requirement of Annex IX, 8.7.2. However, the additional investigations proposed by the Registrant in order to confirm and further investigate the identified concern on peri- and post-natal reproductive toxicity do not fall within the scope of a pre-natal developmental toxicity study as described in the OECD 414/EU B.31 test method. ECHA notes however that a screening study according to the OECD test guideline 421/422, modified as appropriate to address the Registrant's specific concern, may provide useful information in relation with the above-mentioned concern. ECHA further outlines that the above mentioned concerns could be investigated by the reproductive toxicity study, in accordance with Annex IX, 8.7.3. The Registrant should therefore consider whether investigations on the reproductive toxicity of the registered substance are required in accordance with the provisions of Annex IX, 8.7.3 and submit a testing proposal if deemed appropriate.

As a conclusion, ECHA agrees with the Registrant's proposal to perform a pre-natal developmental toxicty study according to the standard protocol described in the OECD 414 test guideline in order to meet the information requirement of Annex IX, section 8.7.2. It is at the Registrant's responsibility and discretion to further address any remaining concerns.

ECHA reserves the right to further investigate this concern in relation to the standard information requirements.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) without the proposed inclusion of additional satellite groups.

IV. Adequate identification of the composition of the tested material

It is important to ensure that the particular sample of substance tested in the new study 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. 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation E1

[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.