EUROPEAN CHEMICALS AGENCY

Helsinki, 28 May 2019

Addressee: [redacted]

Decision number: TPE-D-2114470982-39-01/F
Substance name: Ethylene dibenzoate
EC number: 202-338-6
CAS number: 94-49-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/02/2018
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

1. **Developmental neurotoxicity study, oral route (Annex IX, Section 8.6.2., Column 2; test method: OECD TG 426) in rats using the registered substance; and**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

You have to submit the requested information in an updated registration dossier by **4 June 2021**. You also have to update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by **Ofelia Bercaru**, Head of Unit, Hazard Assessment C4

[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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

1. Developmental neurotoxicity study (Annex IX, Section 8.6.2., Column 2)

a) Examination of the testing proposal

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

According to Column 2 of Annex IX, Section 8.6.2., *'Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 in case of:*

- *failure to identify a NOAEL in the 90 days study unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects, or*
- *toxicity of particular concern (e.g. serious/severe effects), or*
- *indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation. In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity), or*
- *particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected)'.*

You have submitted a testing proposal for a developmental neurotoxicity study in rats according to OECD TG 426 by the oral route. You justify that further testing is necessary as follows: *'In a combined OECD 422/408 study at 1000 mg/kg bw/d decreased T4 levels (for females in combination with increased incidence of follicular cell hypertrophy in the thyroid) at 1000 mg/kg, of which adversity could not be excluded was observed. In females treated at 1000 mg/kgmicroscopic examination revealed an increased incidence of follicular cell hypertrophy (minimal or slight) in the thyroid. This was accompanied by a decrease of thyroid hormone T4 (on average 19%). In males treated at 1000 mg/kg serum levels of thyroid hormone T4 were also decreased (on average by 57%), unaccompanied by treatment related changes in thyroid weight or morphology. For both males and females no corroborative findings were observed in TSH levels. Based on these findings, referring to Draft Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 16 528/2012 and (EC) No 1107/2009 (December 2017), these effects may indicate a hazard for human throid insufficiency in adults as well as pre- and post-natal neurological development of offspring. An OECD 426 is proposed as a follow up study to further evaluate the potential neurodevelopmental effects.'*

ECHA agrees that you have identified a concern for thyroid disruption in repeated-dose toxicity, and this is indeed an indication of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation; specifically, that thyroid insufficiency could lead to developmental neurotoxicity. As it was mentioned before, according to Column 2 of Annex IX, Section 8.6.2. in such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects. The Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a[2] lists the OECD TG 426 developmental neurotoxicity study as an alternative

[2] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, Version 6.0, Page 426.

that provides information on repeated dose toxicity.

ECHA requested your considerations for alternative methods to fulfil the information requirement for further toxicity studies with regard to developmental neurotoxicity: ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that a Developmental neurotoxicity study performed with the registered substance is appropriate to address the identified concerns with regard to thyroid disruption as required by the Column 2 requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 426, the rat is the preferred species. On the basis of this default consideration, ECHA considers testing should be performed with rats. With regard to which rat strain to use, it should be highlighted that the OECD TG 426 state that: *'If there was an earlier test that raised concerns, the species/strain that raised a concern should be considered. Because of the differing performance attributes of different rat strains, there should be evidence that the strain selected for use has adequate fecundity and responsiveness.'*

You did not specify the route for testing.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party argues that there are no concerns for developmental neurotoxicity because no neurotoxicity was observed in the available study.

ECHA considers that developmental neurotoxicity (in peri- and neo-natal animals) and neurotoxicity (in adult animals) are two separate endpoints. Futhermore, ECHA considers that concerns for thyroid disruption has been identified in the same study (reduction of thyroid hormones and hyperthropy of the thyroid). Such effects may indicate a hazard for human thyroid insufficiency in adults as well as during pre- and post-natal neurological development. Therefore, ECHA considers that the information provided by the third party is insufficient to demonstrate that the Column 2 of Annex IX 8.6.2. requirements for further testing to address specific toxicological concerns are not met.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision:

Developmental neurotoxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 426).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that a pre-natal developmental toxicity study study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You did not specify the route for testing.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 14 March 2018.

ECHA held a third party consultation for the testing proposals from 21 May 2018 until 5 July 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **13 March 2019**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your 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.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported 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 the substance tested in the new tests 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 or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.