EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350478-43-01/F
Substance name: Oxydipropyl dibenzoate
EC number: 248-258-5
CAS number: 27138-31-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 02.12.2015
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **21 June 2018**. You shall also update the chemical safety report, where relevant.

The scope of this compliance check decision is limited to the standard information requirement(s) of Annex IX, Sections 8.7 of the REACH Regulation.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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, Evaluation E3

[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

Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement according to Annex X, Section 8.7.2., column 2. You provided the following justification for the adaptation:

"*For reproductive toxicity tests under Sections 8.7 of Annexes IX and X of the REACh Regulation (Regulation), Column 2 provides that studies do not need to be conducted if the substance is of low toxicological activity (i.e., no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*

For pre-natal developmental toxicity studies under Section 8.7.2 in Annex IX, the Regulation requires a study (OECD 414) in one species using the most appropriate route of administration having regard to the likely route of human exposure. For substances manufactured or imported in quantities of 100 tonnes or more (Annex IX) or 1000 tonnes or more (Annex X), Column 2 requires the registrant to make a decision on the need to perform another pre-natal developmental study on a second species based upon the results of the first study and all other relevant data.

Following a careful review of the prenatal developmental toxicity study in the first species and all other relevant data for dipropylene glycol dibenzoate (DPGDB) in accordance with the specific rules set forth in Column 2, the Lead Registrant has determined that performing another pre-natal developmental study in a second species is not warranted. Specifically, the existing data from a prenatal developmental toxicity (OECD 414) study and a 2-generation reproductive toxicity (OECD 416) study in rats indicate that no evidence of developmental toxicity was observed.

Based on these results, the LR concludes that there is no data suggesting that developmental toxicity is a concern and that a pre-natal developmental toxicity study using a second species is not warranted. Thus, the LR will not perform another OECD 414 study in a second species under Annex X.

Furthermore, this decision to not conduct additional animal testing is consistent with the objective of Article 25 which stresses that animal testing under the Regulation shall be undertaken only as a last resort and that it is necessary to take measures to limit duplication of other tests. The decision to not conduct an additional OECD 414 study is well justified by the existing data, including the existing OECD 414 study, and to resort to additional testing would be adverse to the objectives of Article 25."

You also have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2.

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2 or the general rule for adaptation of Annex XI, Section 1.2. for the following reasons:

Concerning the first point of your adaptation justification, in the subchronic toxicity study effects were seen in the liver and in the prenatal developmental toxicity study effects were seen in the CD rat and they occurred in absence of maternal toxicity. Therefore, the column 2 adaptation of low toxicological activity or no absorption is not valid. Based on the dossier, the substance is used in coatings, lubricants, adhesives, sealants and inks and it has several professional and consumer uses. Therefore, one cannot assume that the human exposure is not significant.

With regard to the second point, that is deciding on the need for testing on a second species, this adaptation applies at Annex IX, whereas this substance is at Annex X.

In the third point, you argue that the available OECD 414 and OECD 416 show no indications of developmental effects and therefore a further study is not needed. However, these studies were conducted with rats, so no conclusions can be drawn for non-rodent species.

The fourth point concerning the claim of absence of developmental effects is not true as effects were reported (From the dossier section 7.8.2 ([redacted] 1998) "Details on embryotoxic/teratogenic effects"): *"An association between treatment at 1000 and 500 mg/kg/day and the greater number of fetuses with incomplete ossification of the 5th and or 6th sternebrae cannot be discounted particularly since a delay in ossification would be expected to be the most sensitive marker of an effect on pre-natal development where treatment has continued through to the day before sacrifice (treatment period: Days 6 to 19 of gestation). The assessment of fetal ossification on Day 20 of gestation represents a snapshot in time as the ossification will continue as the animals grow and mature. The increase in cervical ribs at 1000 mg/kg/day is considered to be of greater toxicological significance as it occurred at a dosage which has not produced any detectable signs of maternal toxicity however cervical ribs were only found in a small number of fetuses (10/155) at the limit dosage of 1000 mg/kgl/day and there was no concomitant change in vertebral configuration."*

With regard to the last paragraph of your justification and its reference to Article 25(1) of the REACH Regulation, performing a prenatal developmental toxicity study in a second species cannot be considered as duplication of tests as one species can be more sensitive than another and the legislator has codified a requirement of two species at the highest tonnage level. Moreover, the results of the rat study indicate that performing a test in a second species could have been justified already at a lower tonnage level.

Hence, ECHA cannot follow your individual arguments to adapt the information requirement. These independent sources of information cannot be used jointly either to assume/conclude that the substance in question has or has not a particular property for pre-natal developmental toxicity in the rabbit based on a weight of evidence approach (Annex XI, 1.2 of the REACH Regulation). ECHA considers that because there is no information or indications thereof on the pre-natal developmental effects for rabbit which is required for your respective tonnage level, even when taking all elements together, the weight of evidence approach fails to address the information requirement for prenatal developmental toxicity in rabbit.

Therefore, ECHA considers that the requirements of Annex XI, 1.2 are not fulfilled and your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbits) by the oral route.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline with 9 additional months, poiting out unforseen complications and delays relating to severe inappetance caused by gastric irritation. ECHA considers that 18 months is sufficient time to conduct a prenatal developmental toxicity study and the associated dose-range finding and palatability studies. Therefore, your deadline is extended with an additional 6 months to the original 12 months to a total of 18 months.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 18 February 2016.

ECHA notified you of the draft decision and invited you to provide comments.
ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. 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 your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) 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 test(s) to be assessed.