ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000003056-80-05/F Helsinki, 15 March 2013

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

For Benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate, CAS No 16883-83-3 (EC No 240-920-1), 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 proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate, CAS No 16883-83-3 (EC No 240-920-1), by [redacted] (Registrant).

- Prenatal developmental toxicity study (OECD Guideline 414) in rats by oral route, with substance 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl;
- Two-generation reproduction toxicity study (OECD Guideline 416) in rats by oral route, with substance 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl.

The present decision relates to the examination of the testing proposals for a pre-natal developmental toxicity study. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 2 November 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.

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.

On 9 November 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 16 June 2011 until 1 August 2011. ECHA did receive information from third parties (see section III below).

On 4 January 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 (based on submission number [redacted]).

On 2 February 2012 ECHA received comments from the Registrant to ECHA's draft decision. On 2 March 2012 the Registrant updated his registration dossier (submission number [redacted]).

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III) whereas no amendments to the Testing Required (Section II) were made.

On 2 November 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 5 December 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.

ECHA reviewed the proposals for amendment received and decided not to amend the draft decision.

On 17 December 2012 ECHA referred the draft decision to the Member State Committee.

On 20 December 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study (Annex X, 8.7.3) and one relating to the testing proposal for a pre-natal developmental toxicity study.

A unanimous agreement of the Member State Committee on the draft decision relating to the testing proposal for a pre-natal developmental toxicity study was reached on 21 January 2013 in a written procedure launched on 11 January 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

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

1. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2., test method: EU B.31/OECD 414);

while the originally proposed tests for a study with test method: OECD 414/Prenatal developmental toxicity study and OECD 416/Two generation reproduction toxicity study proposed to be carried out using substance 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl are rejected pursuant to 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 **17 March 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2 of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7 column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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 submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Pre-natal developmental toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance with the testing proposal with Annexes IX, X and XI of the REACH Regulation.

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 proposed testing with substance 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl. In the submission [redacted] on which the decision sent to the Registrant was based, the Registrant justified the proposed read-across by stating that the substance to be tested is the closest structural analogue of the registered substance commercially available. The Registrant did not further justify the proposed read-across with any comparison of the chemical structures and toxicological properties of the registered substance and the substance to be tested.

If the Registrant suggests carrying out the proposed test required by Annex IX on another substance than the registered substance, Article 13(1) and Annex IX, third introductory paragraph, require the Registrant to clearly state reasons for adapting the standard information according to the rules in Annex XI. Accordingly, the similarity between the registered substance and the substance to be tested needs to be established by the Registrant. The Registrant did not provide any comparison between registered substance and the substance to be tested nor sufficient information on the identity and concentration of different constituents or groups of constituents (including information on (stereo)isomers if applicable) which these two substances consist of and/or relevant impurities. The information on substance identity provided for the registered substance and the substance to be tested is not adequate or sufficient to enable a reliable comparison between the two substances.

Annex XI, section 1.5 also provides that substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. However, the application of the group approach requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) by interpolation to other substances in the group (read-across approach). Furthermore, Annex XI requires also that the documentation of the applied method is adequate and reliable. ECHA points out that the Registrant did not provide adequate documentation of the applied method and it is therefore not clear from the registration dossier on which grounds listed in Annex XI, section 1.5 governing grouping of substances and read-across the proposed read-across is based on. As the read-across justifications provided by the Registrant in submission [redacted] were not robust enough to allow the conclusion that the requirements of Annex XI, 1.5 are met, ECHA concluded that this is not a sufficient basis to fulfil the information requirement by testing substance 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl. Therefore, the proposed test was rejected pursuant to Article 40(3)(d) of the REACH Regulation.

In his official comments to the draft decision and the consequent dossier update the Registrant submitted a more detailed justification for read-across. The Registrant also included a comparison of the structures, toxicities and physico-chemical properties of the registered and source substances as well of two other analogues.

However, ECHA notes that an important structural difference i.e. the presence of an additional ester group in the non-benzylic side chain of the registered substance but not in the non-benzylic side chain of the substance to be tested is not addressed in the read-across justification provided by the Registrant. ECHA points out that the possibility of a significant influence of this difference on toxicokinetics and toxicodynamics of these two substances, in particular the influence on the toxicological endpoint for which the read-across is performed, cannot be excluded.

ECHA notes further that the two non-benzylic side chains also differ due to the moiety between the two ester bonds in the side chain of the registered substance. This difference also deserves consideration because of the steric hindrance and its molecular volume in the vicinity of the benzylic ester group. The Registrant has not addressed this difference.

It is unclear which mono ester is formed during metabolism from the registered substance and its analogue, whereby there is a possibility for the formation of a monoester with a primary alcohol group for the registered substance.

These differences invalidate the general observations on phthalate ester toxicity and the relationship between the chemical structure of these compounds and their reproduction toxicity. This prevents confirming the worst-case argument made by the registrant.

In addition, the perceived similarity in physico-chemical properties among the four phthalates considered in the Registrant's updated justification does not support the read-across as long as the relationship between these properties and the toxicological effect to be read across is not explained.
Finally, the argument that the read-across is supported by the presumed low or absent effects for other toxicological endpoints than the one for which the read-across is proposed, is not adequate, as the relationship between the other endpoints and the endpoint covered by the read-across is not explained. Moreover, the known reproductive toxic phthalate esters also show a low toxicity for these other endpoints.

ECHA thus concludes that the justifications do not allow determining that the properties concerning Pre-natal developmental toxicity of the registered substance can be reliably predicted from the data generated by a test to be performed with the proposed analogue substance. The requirements of Annex XI, section 1.5 in conjunction with Article 13(1) and Annex IX, third introductory paragraph are not met and the read-across approach is not justified Therefore, the proposed test using read-across to an analogue is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

The Registrant proposed testing in rat by oral route. 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 rabbit as a first species to be used.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.

b) Consideration of third party information

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

The third party has proposed to use a result of the QSAR model Nonlinear classification ANN QSAR Model for prenatal developmental toxicity study. The third party has indicated that their information is confidential and this information is not provided to the Registrant.

The result from the QSAR classification model (i.e. "toxic" or "non-toxic") is not suitable for the purposes of classification and labelling and/or risk assessment for the endpoint for which testing has been proposed to meet the information requirement (Annexes IX or X, 8.7.). Compliance with the Annex XI section 1.3 requirements could not be established as the required information concerning the validity, adequacy for classification and labelling and documentation of the model was not provided. The (Q)SAR Model Reporting Format (QMRF) does not provide sufficient information to deduce whether the training set was constructed from studies that cover the information requirements of the OECD 414 guideline, or important study aspects, such as the species, dose selection and number of animals used. In addition the

submitted QPRF does not contain any indication on the adequacy in relation to a defined regulatory purpose of the testing proposal.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of QSAR models set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

d) Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a reproductive toxicity study according to the standard information requirement of Annex X, 8.7.3 of the REACH Regulation. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 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. If the registration of the substance covers different grades, the sample used for the new studies 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 studies to be assessed.

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 reads:

> "*Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.*"

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 other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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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