EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114292038-46-01/F Helsinki, 5 February 2015

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For Dibutyl fumarate, CAS No 105-75-9 (EC No 203-327-9), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for Dibutyl fumarate, CAS No 105-75-9 (EC No 203-327-9, submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirements of Annex IX, Sections 8.6.2 and 8.7.2 of the REACH Regulation. ECHA has not checked the information provided by the Registrant and other joint registrants for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100-1000 tonnes per year. This decision does not take into account any updates submitted after 30 October 2014, 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

The compliance check was initiated on 30 May 2013.

On 26 September 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted]

On 21 October 2013 ECHA received comments from the Registrant on the draft decision.

On 11 September 2014 the Registrant updated his registration dossier with the submission number [redacted]

ECHA considered the Registrant's comments received and update received. On the basis of the comments and update, Section II of the draft decision was not amended. The Registrant's comments on the draft decision and ECHA's responses are reflected in Section III of the draft decision.

On 30 October 2014 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(d), 13 and Annex IX of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;

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

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit to ECHA by **13 February 2017** an update of the registration dossier containing the information required by this decision.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vii), 12(1)(d) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annex IX of the REACH Regulation.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.)

A "Sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has not provided any study record of a sub-chronic repeated dose toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

The Registrant has justified the proposal for adaptation without specifying the adequate adaption possibility given in the respective column 2 of that section of Annex IX. The Registrant has referred to low potential of absorption, low toxicity and practically no exposure to the substance.

According to Annex IX, 8.6.2., Column 2, no sub-chronic toxicity study needs to be conducted if "the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure."

The Registrant has however not adequately shown that the conditions of the above mentioned adaptation possibility are fulfilled. In addition, ECHA notes that no 28-day study record/data was provided in the registration dossier. It has not been documented that there is "no systemic absorption via relevant routes". According to the process descriptors provided by the Registrant, there is potential for exposure.

Therefore, since the Registrant has not provided sufficient information to show that conditions of an adaptation in Column 2 of Annex IX, 8.6.2. are met, the adaptation of the information requirement proposed by the Registrant cannot be accepted.

Furthermore, the Registrant has not provided any study record of a sub-chronic repeated dose toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

As explained above, the information available 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.

In the comments to the draft decision, the Registrant proposed as a first option to perform a 28-day short-term repeated dose toxicity study with the registered substance dibutyl fumarate (DBF) and to cover the information requirement for the 90-day sub-chronic toxicity study with data on the read-across (RA) substance dioctyl fumarate (DOF). The dossier update (dated 11 September 2014) includes no data on repeated dose toxicity of the two substances.

To support the read-across, the Registrant has provided relevant data on the structure of the source substance of the read-across (RA) Dioctyl fumarate (DOF) and on the structure of the target substance Dibutyl fumarate (DBF). Furthermore the Registrant provided a matrix, which includes basic physico-chemical data and acute toxicity as well as skin and eye irritation/corrosion and skin sensitisation studies on DBF and DOF.

However, the proposed read-across is not sufficiently developed, since several essential elements of the RA justification and documentation are missing. No read-across hypothesis has been provided and furthermore, the Registrant has not explained how the properties of the target substance Dibutyl fumarate can be predicted from the information on source substance Dioctyl fumarate.

Relevant toxicokinetic data is not available but the Registrant suggests that he will provide them later. In the dosser update submitted 11 September 2014 (submission number [redacted]) that data was not provided.

The acute toxicity, skin and eye irritation/corrosion and sensitisation data do not support read-across, because the target substance (DBF) seems to be more reactive and more toxic than the source substance (DOF). Therefore, one-to-one read-across from DOF to DBF is not considered plausible. Furthermore, the Registrant has not explained how the data on metabolism could be used to further justify the read-across and to predict the properties of seemingly more toxic target substance of the read-across.

ECHA concludes that the information provided in the comments on the draft decision is not sufficient to adapt the standard information requirement for a sub-chronic toxicity study.

Therefore, pursuant to Article 41(3) of the REACH Regulation, the Registrant is requested to submit information on sub-chronic toxicity (90-day) (Annex IX, Section 8.6.2.) using the registered substance. In light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate. Therefore the Registrant shall use test method (EU B.26 OECD 408). According to the test method the rat is the preferred rodent species. ECHA considers this species as being appropriate.

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

The Registrant has justified the proposal for adaptation with a reference Annex IX, section 8.7. column 2. The Registrant has referred to low toxicity and no human exposure to the substance.

According to Annex IX, 8.7., Column 2, the study does not need to be conducted if the substance is of "low toxicological activity", "no systemic absorption via relevant routes of exposure" and there is "no or no significant human exposure" .

The Registrant has however not adequately shown that the conditions of that adaptation possibility are fulfilled. It has not been documented that there is no systemic absorption via relevant routes. According to the process descriptors provided by the Registrant, there is potential for exposure.

Therefore, since the Registrant has not provided sufficient information to show that conditions of an adaptation in Column 2 of Annex IX, 8.7 are met, the adaptation of the information requirement proposed by the Registrant cannot be accepted.

As explained above, the information available 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.

In the comments to the draft decision, the Registrant proposed as *a first option* to perform a 28-day short-term repeated dose toxicity study with the registered substance dibutyl fumarate (DBF) and to cover the information requirement for the 90-day sub-chronic toxicity study with data on the read-across (RA) substance dioctyl fumarate (DOF). If no indications are found for reproduction toxicity in all available data sources the Registrant intends to waive the pre-natal developmental toxicity study.

To support the read-across, the Registrant has provided relevant data on the structure of the source substance of the read-across (RA) Dioctyl fumarate (DOF) and on the structure of the target substance Dibutyl fumarate (DBF). To the extent that concerns the proposed read-across, the response given above on sub-chronic toxicity applies.

Furthermore, ECHA notes that DOF and DBF are metabolised to two different metabolites, n-butanol and ethyl-hexanol. Publicly available data indicates that both of these alcohols may cause developmental toxicity (at least in high doses). This has not been considered by the Registrant; on the contrary the Registrant appears to assume that "no indications are found for reproduction toxicity in all available data sources."

Concerning the waiving approach proposed by the Registrant, which is consequent to the read-across, i.e. "Waiving OECD 414 if no indications are found for reproduction toxicity in all available data sources", ECHA notes that REACH Regulation does not allow that kind of adaptation.

As *a second option*, the Registrant proposes to "Perform 90 day oral repeated dose study with DBF (OECD 408), with extra histopathology on reproduction toxicity parameters; waive OECD 414 if no indications for reproduction toxicity are found." ECHA notes that because a sub-chronic study, even if extended as proposed by the Registrant, only partly covers the observations and parameters of pre-natal development toxicity (as in the OECD TG 414) that adaptation is not acceptable.

ECHA concludes that the information provided in the comments on the draft decision is not sufficient to adapt the standard information requirement for a pre-natal developmental toxicity study.

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.

Therefore, pursuant to Article 41(3) of the REACH Regulation, the Registrant is 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 414) in rats or rabbits by the oral route.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, 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 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 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

V. 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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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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