Decision number: CCH-D-2114288751-40-01/F Helsinki, 12 December 2014

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

For dibutyl maleate, CAS No 105-76-0 (EC No 203-328-4), 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 maleate, CAS No 105-76-0 (EC No 203-328-4), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirements of Annex IX, Section 8.7.2 of the REACH Regulation. ECHA stresses that it 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 1000 tonnes or more tonnes per year. This decision does not take into account any updates submitted after 12 June 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 25 October 2013.

On 28 November 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 13 January 2014 ECHA received comments from the Registrant on the draft decision. On 14 January 2014 the Registrant updated his registration dossier with the submission number [redacted]. The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 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.

Subsequently, proposals for amendment to the draft decision were submitted.

On 18 July 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and did not amend the draft decision.

The draft decision was split into two draft decision documents: one relating to the request for a two-generation reproductive toxicity study and one relating to the request for a pre-natal developmental toxicity study.

The present decision relates solely to compliance checks for a pre-natal developmental toxicity study. The other compliance check requirement of a two-generation reproductive toxicity study (Annex X, 8.7.3) is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

On 28 July 2014 ECHA referred the draft decision to the Member State Committee.

By 18 August 2014 in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision relating to a pre-natal developmental toxicity study was reached on 1 September 2014 in a written procedure launched on 21 August 2014.

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

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes IX and X 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:

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

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **21 December 2015**.

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 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 the Member States.

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)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

The Registrant provided comments to the draft decision and updated the registration. In the updated registration, the Registrant has adapted the standard information requirements for the pre-natal developmental toxicity study (Annex IX, 8.7.2.) by applying a read-across adaptation following REACH Annex XI, Section 1.5. The read-across approach is reflected in the following section.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

The Registrant selected butyl hydrogen maleate, maleic acid, and maleic anhydride as the most suitable read across substance for dibutyl maleate as they represent metabolic or chemical breakdown products of dibutyl maleate. Butyl hydrogen maleate is the initial product resulting from the action of esterases *in vivo*, and can also result from chemical hydrolysis under certain conditions. Butyl hydrogen maleate retains one ester moiety, and re-introduces one of the carboxylic acid moieties that were present in the raw material. Maleic acid results from the complete de-esterification and/or chemical hydrolysis of dibutyl maleate. Because of its high reactivity with water, maleic anhydride is rapidly converted to maleic acid in biological systems.

The Registrant compared the effects in dibutyl maleate, butyl hydrogen maleate, and maleic anhydride/maleic acid and concluded that all substances cause similar renal effects and can thus be used as read across substances (similarities in mode of action).

The Registrant assumes that in the case of dibutyl maleate and butyl hydrogen maleate, reproductive effects, if any, would be related to the maleic acid anion, which is the core structure for dibutyl maleate, butyl hydrogen maleate, and maleic anhydride. The corresponding linear alcohol n-butanol does not reveal any adverse effects on reproduction and development.

b. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

In the initial registration on which the draft decision sent to the Registrant was based, the Registrant has provided a study record for a OECD 422 screening study performed with the registered substance. On basis of this study, the Registrant had waived the requirement for the pre-natal developmental toxicity study.

In the updated registration, the Registrant provided a study record of a publication on "Teratology and multigeneration reproduction studies with maleic anhydride in rats" (Short et al. 1986) to fulfil the endpoint pre-natal developmental toxicity.

The Registrant has provided a read-across document with the comments on the draft decision. In this read-across document the following arguments were provided by the Registrant to justify the read-across approach:

i. Structural Similarity and Common breakdown products

The Registrant indicated that dibutyl maleate is synthesized [redacted]. Therefore, these substances form the core of the final product, which is a diester ([redacted]). While the diester lacks the functional groups of the precursor molecules (carboxylic acid and primary alcohol), *in vivo* metabolism via esterases results in the production of these precursor substances and their functional groups. As expected from steric hindrance and thermodynamic consideration, breakdown of the diester occurs via the monoester stage. The Registrant concludes that the maleic substructure is the relevant core structure for dibutyl maleate, butyl hydrogen maleate, and maleic anhydride.

The Registrant expects that diesters undergo hydrolysis in mammals, producing the corresponding alcohol and acid. These substances are further metabolized and excreted mainly in the urine (Parkinson, 2008). The Registrant concludes that hydrolysis data indicate that both the monoester and acid can be present in the body. The diester is readily broken down to the monoester and eventually the acid. These considerations and data justify use of maleic acid data.

The Registrant expects that maleic acid structure is present in mammals and is expected to be the relevant acting agent because maleic anhydride is readily hydrolyzed to maleic acid under aqueous conditions. As a result, these two chemicals are presented because of the conditions used to test their toxicity" (OECD, 2004). Maleic anhydride data are presented in the read across rationale. Since maleic anhydride is rapidly converted into maleic acid (OECD, 2004), the Registrant expected that when testing the anhydride, the effects are caused by the acid due to the similar structural activity (SSA).

Comparing effects in dibutyl maleate, butyl hydrogen maleate, and maleic anhydride/maleic acid shows the Registrant concludes that all substances cause similar renal effects (i.e. the same pattern of toxicological activity) and can thus be used as read across substances because they fulfil the criterion "*The similarities may be based on: [...] (2) [...] or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals;*" (REACH Annex XI, Section 1.5.) Therefore, maleic anhydride can be regarded as suitable for read across, but shows no developmental or reproductive effects. Thus, he concludes that the same is valid for dibutyl maleate. In the case of dibutyl maleate and butyl hydrogen maleate, reproductive effects, if any, would be related to the maleic acid anion, which is the core structure for dibutyl maleate, butyl hydrogen maleate, and maleic anhydride. The corresponding linear alcohol n-butanol does not reveal any adverse effects on reproduction and development.

ii. Toxicologiocal effects

The Registrant assumes that substances with similar structural activity (SSA) are expected to have similar systemic toxicity on specific target organ(s). Dibutyl maleate, maleic anhydride/maleic acid and butyl hydrogen maleate show similar structural activity. Data for dibutyl maleate and similar substances show consistently low acute toxicity and negative mutagenicity. In addition, the systemic toxicity of dibutyl maleate in the kidneys is consistent with substances with similar functional chemical groups (Table 1 of the read-across rationale). In addition, these substances did not show developmental and/or reproductive toxicity in repeated dose and developmental or reproductive animal studies. Because of the similarity in functional and morphological changes in the kidneys observed in the animal studies (see Table 1 of the read-across rationale) the Registrant selected maleic anhydride/maleic acid and butyl hydrogen maleate as suitable substances for read across evaluation to fulfil developmental and reproductive data gaps in the dibutyl maleate REACH registration.

The Registrant assumes that in the case of dibutyl maleate and butyl hydrogen maleate, reproductive effects, if any, would be related to the maleic acid anion, which is the core structure for dibutyl maleate, butyl hydrogen maleate, and maleic anhydride. The corresponding linear alcohol n-butanol does not reveal any adverse effects on reproduction and development. No documentation to support the above assumption was provided.

c. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

i. Structural Similarity and Common breakdown products

ECHA notes that the Registrant has cited that metabolism of diesters in animals would be expected to occur initially via enzymatic hydrolysis leading to the corresponding diacids (e.g. maleic acid) and branched alcohols (e.g. n-butanol). Furthermore, ECHA notes that in the registration, the Registrant has cited information on hydrolysis of dibutyl maleate with hydrolysis occurring to the monoester only in the alkaline saliva simulant (pH 9) but not under neutral conditions (pH 7.5) or strong acidic conditions (pH 1.2). However, the Registrant did not provide any documentation to demonstrate enzymatic hydrolysis of dibutyl maleate.

ii. Toxicologiocal effects

ECHA notes that based on the information provided on similarity of the structure and based on the results from repeated dose toxicity studies described in the read-across document,

the substances seem to have a similar mode of action. In more detail, the NOAELs for the repeated dose toxicity studies considered for read-across are in a similar range all leading to kidney toxicity: 30 mg/kg bw/d in a 90-day repeated dose toxicity study with dibutly maleate; 40 mg/kg bw/d in a 90-day repeated dose toxicity study with maleic anhydride/maleic acid; and 100 mg/kg bw/d in an OECD 422 screening study with butly hydrogen maleate. Therefore, ECHA acknowledges that the substances seem to have a similar mode of toxicological action.

d. ECHA analysis of the endpoint-specific read-across approach in light of the requirements of Annex XI, 1.5.

i. Reproductive toxicity

The Registrant has provided a study record of a "Teratology and multigeneration reproduction studies with maleic anhydride in rats". In this study, maleic anhydride showed effects on the kidney but did not show developmental or reproductive effects. Even if the study is from the year 1986, ECHA notes that the study is sufficient to cover the information requirement for a pre-natal developmental toxicity study. The Registrant concludes that maleic anhydride is suitable for read across based on a similar mode of action for kidney toxicity. ECHA notes that the Registrant has provided a study record for a OECD 422 screening study performed with the registered substance that confirmed the systemic effects on the kidneys and the absence of signs of developmental or reproductive toxicity. Therefore, ECHA acknowledges that the developmental or reproductive effects might be predicted from maleic anhydride to the registered substance.

The Registrant further concludes that the corresponding linear alcohol n-butanol does not reveal any adverse effects on reproduction and development. However, ECHA notes that the Registrant did not provide any documentation to demonstrate that n-butanol does not reveal any adverse effects on reproduction and development.

e. Conclusion on the read-across approach

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoint pre-natal developmental toxicity in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. More specifically, (i) the Registrant did not provide any documentation to demonstrate enzymatic hydrolysis of dibutyl maleate and (ii) the Registrant did not provide any documentation to demonstrate that the metabolite n-butanol does not reveal any adverse effects on reproduction and development. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

1. 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.

In the updated registration, the Registrant has adapted the standard information requirements for the pre-natal developmental toxicity study (Annex IX, 8.7.2.) by applying a read-across adaptation following REACH Annex XI, Section 1.5. The Registrant has provided a study record of a publication on "Teratology and multigeneration reproduction studies with maleic anhydride in rats" (Short et al. 1986).

ECHA has evaluated the Registrant's read-across approach and concluded that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above) as:
(i) The Registrant did not provide any documentation to demonstrate enzymatic hydrolysis of dibutyl maleate.
(ii) The Registrant did not provide any documentation to demonstrate that the metabolite n-butanol does not reveal any adverse effects on reproduction and development.

To conclude, the criterion that need to be met for a read-across adaptation to be possible, namely to provide adequate and reliable documentation is not met.

Therefore, the adaptation of the information requirement suggested 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.

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(1) and (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.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

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; 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. 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. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2

2. 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 addresed a two-generation reproductive toxicity study (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration 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

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.

[redacted]

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