EUROPEAN CHEMICALS AGENCY

Decision number CCH-D-0000003029-77-04/F Helsinki, 14 March 2013

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

For Bis(2-ethylhexyl) adipate, CAS No 103-23-1 (EC No 203-090-1), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for Bis(2-ethylhexyl) adipate, CAS No 103-23-1 (EC No 203-090-1) submitted by [redacted] (Registrant).

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 compliance check decision does not prevent ECHA to initiate further compliance checks on the registration at a later stage.

The compliance check was initiated on 22 March 2011.

On 22 March 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.

On 19 April 2012 ECHA received comments from the Registrant. On 22 May 2012 the Registrant updated his registration dossier.

ECHA considered the Registrant's comments and dossier update received. On the basis of the comments, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

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, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 5 December 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal 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 18 December 2012 the Registrant provided comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 5-7 February 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 6 February 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1)(a), 41(3), 10(a)(vi), 12(1)(e), and Annex X of the REACH Regulation the Registrant shall submit the following information using the registered substance and the test method as indicated on:

- A pre-natal developmental toxicity study in rabbit by the oral route (Annex X, 8.7.2.; test method B.31 /OECD 414).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **14 March 2014**.

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

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance for the purpose of registration within the applicable tonnage band of above 1000 tonnes per year in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles 10 and 12 and Annexes I, VII and X of the REACH Regulation. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vi) and 12(1)(e) of the REACH Regulation, a registration for a substance produced in quantities above 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

The technical dossier did not contain any information or valid adaptation to the standard information requirement for the endpoint on a pre-natal developmental toxicity study in a second species (Annex X, 8.7.2.).

A developmental toxicity study for a second species is a standard information requirement for substances manufactured in quantities of 1000 tonnes or more as laid down in Annex X, section 8.7.2 of the REACH Regulation.

Annex IX, section 8.7.2 describes the information requirement for a pre-natal developmental toxicity study on the first species with the following column 2 provision: "The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data." Annex X, section 8.7.2 has a separate, and additional, column 1 information requirement for "Developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (OECD 414)." Both information requirements are subject to all appropriate column 2 or Annex XI data adaptations.

Also the ECHA guidance on information requirements and chemical safety assessment (Chapter R.7a endpoint specific guidance, R7.6.6.3) indicates the need for testing on a second species:" At ≥1000 t/y, a study in a second species will normally be required when the first study is negative, unless Weight of Evidence assessment or specific data e.g. toxicokinetic data provide scientific justification not to conduct the study in a second species. This could be the case if available data demonstrate that for example the rat is the most relevant species for extrapolating to humans or if the rabbit is not a suitable model for testing for developmental toxicity."

ECHA observes that in the technical dossier, the Registrant has provided data (key study) on developmental toxicity in rats by the oral route using the registered substance, bis(2-ethylhexyl)adipate, as test material. Some effects relevant to the prenatal development were observed (reduced ossification, visceral variants) at dose 170 mg/kg b.w./d in this study. The Registrant does not consider these effects as adverse and the NOAEL value was set at the same dose level on the basis of maternal toxicity (reduction in body weight and feed intake). Consequently the Registrant has not self-classified the substance for developmental toxicity. The substance does not have a harmonised classification.

Moreover, Bis(2-ethylhexyl)adipate is metabolized in the body to 2-ethylhexanoic acid (CAS 149-57-5). This metabolite is a suspected teratogen classified as Repr. Cat 2, H361d (CLP-regulation (EC) 1272/2008, Annex VI). Therefore, and in addition to the standard information requirement, also information on the metabolite demonstrates the need to investigate the potential of the registered substance to cause developmental effects in a non-rodent species.

In his comments the Registrant did not agree with the request to conduct a second developmental toxicity study. The Registrant referred to Annex IX, section 8.7.2 which states that "*a need to perform a study on a second species should be based on the outcome of the first test and all relevant available data*". The Registrant provided further justification for why the study is not needed: "*None of the present studies as e.g. acute or repeated dose toxicity (LD50 > 15 g/kg body weight; NOAEL = 200 mg/kg body weight), mutagenicity, carcinogenicity show any health concern. Data from the reproductive toxicity study (OECD 415) showed no effects on male or female fertility, gestation length or pup survival. The observed effects regarding slightly reduced ossification and visceral variants were based on fetotoxicity as it is described in the technical report (CEFIC teratogenicity report, 1988)*". Also with regard to the metabolite 2-ethylhexanoic acid, the Registrant did not agree with the assessment of ECHA that it underlines the need to investigate the parent substance. The Registrant claimed that the metabolite has only minor relevance as it is a

secondary metabolite to the primary metabolite 2-ethylhexanol, which does not have to be classified for developmental toxicity. The Registrant furthermore claimed that high dose levels of 2-ethylhexanol are unlikely since "*excretion is faster than metabolism*".

As stated above, in view of ECHA a second developmental toxicity study is a standard information requirement for registration dossiers at the Annex X tonnage band. The toxicological information provided by the Registrant in his comments does not support adaptation or waiving from this requirement. The first developmental study in rat was negative, which according to the guidance is not a reason to omit the second study. Furthermore, long and short term testing is available on the parent compound (e.g. two carcinogenicity studies). However, due to the design of these studies, the data provided are not adequate to conclude on effects relating to the developmental endpoint. Additionally ECHA is of the opinion that the information on metabolite 2-ethylhexanoic acid provides additional arguments for further testing. Toxicokinetic studies with rats, mice and monkeys demonstrate that 2-ethylhexanoic acid is present in the animals in addition to its glucuronide after exposure to the registered substance; i.e. it is likely present in the organism as free acid and not only as "*a secondary metabolite excreted as glucuronide*". It should also be noted that no quantitative aspects could be deduced from the robust study records because only qualitative profiles of the metabolites identified were presented. Finally, the toxicokinetic data available does not assist in selection of the most appropriate second species for testing of bis(2-ethylhexyl)adipate. 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 any testing should be performed by the oral route with the rabbit as the second species to be used.

Thus the Registrant is requested to submit information on pre-natal developmental toxicity in rabbit by the oral route performed with the registered substance, Bis(2-ethylhexyl)adipate according to EU Method B.31/ OECD test guideline 414.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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

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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