~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: TPE-D-0000001276-76-10/F Helsinki, 16 June 2011

DECISION ON TESTING PROPOSALS PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 12-hydroxyoctadecanoic acid, reaction products with 1,3-benzenedimethanamine and hexamethylenediamine, EC No 432-840-2, 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, Authorisation and Restriction of Chemicals (the REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the testing proposals set out in the registration dossier for **12-hydroxyoctadecanoic acid, reaction products with 1,3-benzenedimethanamine and hexamethylenediamine EC no. 432-840-2** submitted by [redacted] (the "Registrant"), latest submission number [redacted], for [redacted]

The Registrant notified the substance pursuant to the national legislation implementing Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances (as amended) by submitting a notification to the French competent authority in accordance with Article 7 of Directive 67/548/EEC. The notification number allocated was [redacted] Article 24(1) of the REACH Regulation provides that the notification is regarded as a registration and ECHA has assigned a registration number.

In accordance with Article 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier for the provision of the information requirements set out in Annexes IX and X:

- OECD Guideline 211 (Daphnia magna Reproduction Test)
- OECD Guideline 225 (Sediment-Water Lumbriculus Toxicity Test Using Spiked Sediment)
- OECD Guideline 412 (Repeated Dose Inhalation Toxicity: 28/14-Day)

The examination of testing proposals was initiated on 7 April 2010.

ECHA held a public consultation for the testing proposals involving tests on vertebrate animals from 4 May 2010 until 18 June 2010 and received information that addresses the endpoint of repeated dose toxicity, namely the possibility to assess the reaction mixture using publicly available data from pure components. Briefly, the third party mentioned the Annex XI 1.5 criteria for grouping and read-across to justify the read-across from the pure components of the reaction product. Namely 1,3-benzenedimethanamine (one acute inhalation toxicity in the rat), hexamethylenediamine (one acute inhalation study in the rat, one in the mouse, one 3-4 day study in the guinea pig, one in workers, one 9 day study in the rat, one 11-15 day study in the rat, one 4 week study in the rat, one 7-13 week study in the rat) and hexamethylenediamine dihydrochloride (one 12 day study in the rat, one 12 day study in the mouse, one 13 week study in the mouse, one 13 week study in the rat). Furthermore, the comments claim that 12-hydroxy- octadecanoic acid is toxicologically less 'significant' than the other components of the mixture.

The consultation also brought the information that two of the components (1,3-benzenedimethanamine and hexamethylenediamine) are corrosive and referred to the provisions in Annexes IX and X stating that "*in vivo testing with corrosive substances at concentration/dose levels causing corrosivity should be avoided*". More information is provided in the Statement of reasons section below.

On 24 September 2010 ECHA notified the Registrant of its draft decision and invited him to provide comments.

On 22 October 2010, the Registrant provided comments on the draft decision to ECHA, agreeing to the content of the draft decision and asking for an extension of the deadline to submit the requested information by six months to 24 months. ECHA considered the comments provided by the Registrant and did not amend the draft decision.

On 7 January 2011, ECHA notified the Member State Competent Authorities of its draft decision and invited them to provide proposals for amendment on the draft decision.

By 7 February 2011 Member State Competent Authorities had submitted proposals to extend the testing period to 24 months. Based on the proposed amendments, ECHA decided to modify its draft decision.

On 16 February 2011, ECHA notified the Registrant of the proposals for amendment for its draft decision and invited him to provide comments on these proposals.

On 21 February 2011, the draft decision was referred to the Member State Committee.

On 16 March 2011, the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

The amended draft decision was made available to the Member State Committee for agreement seeking in written procedure on 21 March 2011.

Unanimous agreement of the Member State Committee on the amended draft decision was reached on 31 March 2011 by written procedure.

II. Testing required

As proposed, the Registrant shall carry out the following tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test method:

- Long-term toxicity to aquatic invertebrates, Annex IX, Section 9.1.5. (OECD test guideline 211)
- Long-term toxicity to sediment organisms, Annex X, 9.5.1. long-term toxicity to sediment organisms (OECD test guideline 225)

The Registrant shall carry out the following test pursuant to Article 40(3)(c) and (d) of the REACH Regulation using the indicated test method:

- Sub-chronic toxicity study (90-day) in rats, inhalation route, Annex IX, Section 8.6.2. (EU test method B.26 of Regulation (EC) No 440/2008, or OECD 408)

while the proposal for a repeated dose inhalation toxicity: 28/14-Day test is rejected.

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation the Registrant shall submit the information listed above in the form of an updated IUCLID dossier to ECHA by 17 June 2013.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals of the Registrant for the registered substance and the scientific information submitted by third parties.

a) Long-term toxicity to aquatic invertebrates

According to Section 9.1.5 of Annex IX of the REACH Regulation, long-term toxicity testing on aquatic invertebrates is required to fulfil the standard information requirements. As the proposed test for long-term toxicity to aquatic invertebrates is not available for the registered substance but needs to be present in the technical dossier to meet the information requirement of Section 9.1.5 of Annex IX of the REACH Regulation it is necessary to generate the data and to perform the test.

b) Long-term toxicity to sediment organisms

According to Section 9.5.1 of Annex X of the REACH Regulation, long-term toxicity to sediment organisms is required to fulfil the standard information requirements. As the proposed test for long-term toxicity to sediment organisms is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements of Section 9.5.1 of Annex X of the REACH Regulation it is necessary to generate the data and to perform the test.

c) Repeated dose toxicity

The Registrant has submitted a testing proposal to cover the endpoint repeated dose toxicity (OECD 412 guideline) to meet the information requirement of Section 8.6.1 of Annex VIII and Annex IX of the REACH Regulation respectively. Pursuant to Article 12(1)(e) of the REACH Regulation, Registrants are required to provide the information specified in Annexes VII and VIII and testing proposals for the provision of the information specified in Annexes IX and X. Hence, the testing proposal submitted is not appropriate to cover Section 8.6.1. on Annex VIII-level. Whereas at Annex VIII-level, the short-term repeated dose toxicity study (28 days) is a standard information requirement, it is not on Annex IX-level in case it has been already provided as part of Annex VIII requirements or if a testing proposal for the sub-chronic toxicity study (90 days) on Annex IX is made. The legal text however does not foresee that two short-term repeated dose toxicity studies (28 days) are necessary to comply with Annex IX requirements. It becomes clear from the interrelation of Section 8.6.1. in Annex VIII and IX that only one test is required as in Annex IX a clear reference is made to the availability of the study result on the lower Annex VIII-level.

In the case at hand, an oral short-term repeated dose toxicity study (28 days) is available and contained in the technical dossier. If the testing proposal was intended to cover Annex IX, Section 8.6.1. with another route of administration, there appears to be no data gap as the oral study is available and the REACH Regulation does not request a second study to be performed on that endpoint. If the testing proposal was intended to cover Annex IX, Section 8.6.2. (sub-chronic toxicity study (90 days)), it does not meet the requirements of this endpoint due to the length and outline of the study. In a 90 day study the number of animals is higher (10 males and 10 females versus 5 males and 5 females per dose group), ophthalmology is conducted, and more organs are studied for gross pathology and organ weights than in a 28 day study.

According to Section 8.6.2. of Annex IX of the REACH Regulation, a sub-chronic toxicity study (90-day) is required to fulfil the standard information requirements for substances manufactured or imported in quantities of 100 tonnes or more. The Registrant has, however, proposed only a short-term repeated dose toxicity study (28 days) to fulfil the information requirement of section 8.6.1. of Annex VIII/IX mentioned above. Even if the proposal is interpreted as covering as well the endpoint of Section 8.6.2., of Annex IX, no reasoning has been provided by the Registrant why his testing proposal is deviating from the standard information required in Section 8.6.2. of Annex IX of the REACH Regulation. The proposed study therefore does not meet the legal requirements and ECHA has to reject this proposal pursuant to Article 40(3)(d) of the REACH Regulation.

Due to the fact that the sub-chronic toxicity study (90-day) is not available and the effects seen in the submitted acute inhalation toxicity study (harmful by inhalation, Xn; R 20), it is necessary to request a 90-day inhalation study to meet the information requirements and to further investigate the concern raised by the acute inhalation study. This meets as well the requirements of Directive 67/548/EEC Annex VIII Level 1 which provides that '*if other relevant information demonstrate the need for further appropriate investigation*' a 90-day study can be requested. In addition as some toxicity effects (increased liver and adrenal weights, ketones and urine volume increased) were seen in the present 28-day oral study and the Registrant indicates that the inhalation route is more appropriate than oral route for human exposure, it is necessary to further investigate potential toxicity via the inhalation route under a prolonged exposure period.

ECHA has further examined the scientific information submitted by third parties following the public consultation in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoint. This additional information is not, however, able to change the conclusion that a 90-day repeated dose toxicity study needs to be requested, as explained below.

As stated earlier, the toxicological studies submitted by the third party have been generated using substances that are different from the registered substance, namely the three starting materials of the UVCB substance (1,3-benzenedimethanamine, hexamethylenediamine and 12-hydroxyoctadecanoic acid). The read-across approach of Annex XI, Section 1.5. of the REACH Regulation may be used if the physicochemical, toxicological and ecotoxicological properties of the analogue substances are likely to be similar to the ones of the registered substance. However, in the present case, ECHA concludes that the differences between the registered substance and the substances for which the third party submitted the information are significant, whilst also the Annex XI 1.5. criteria for read-across are not met, therefore a read-across approach cannot be applied.

In summary ECHA's examination of the read-across proposal of the third party revealed:

- Differences in the starting materials from the reaction product in terms of functional groups. The starting materials are amines and acid, while the reaction product is amide. The starting materials are also different between themselves: aromatic diamine, aliphatic diamine and aliphatic carboxylic acid. Therefore, structural similarity principle for read-across is difficult to apply. The functional groups of each individual reaction substance may give some indication for behaviour of the reaction mass, but cannot predict reliably the combination of effects caused by the different functional groups in the reaction mass. Thus similarity cannot be based on a common functional group across the category and the criterion of Annex XI section 1.5 point (1) is not fulfilled.
- Differences in the starting materials from the reaction product in terms of physical-chemical properties.
- Differences in the starting materials from the reaction product in terms of ionization potential.
- Differences in the starting materials from the reaction product in terms of bioavailability.
- Differences in the starting materials from the reaction product in terms of toxicological hazard profile. Especially concerning corrosivity there is not a constant pattern in changing of the potency of the properties across the category. Thus the criteria of Annex XI section 1.5 point (3) are not fulfilled.
- No information on the potential metabolic pathway of the reaction product. Thus it is not possible to reliably assess the likelihood of common breakdown products via physical and biological processes and the criteria in Annex XI section 1.5 point (2) are not fulfilled.

The second argument of the third party for the omission of the repeated dose toxicity testing was that "*as 1,3-benzenedimethanamine and hexamethylenediamine are classified as corrosive substances, further testing with the registered substance should be avoided in vivo*". However, in the present case, ECHA concludes that the differences between the registered substance and the substances for which the third

party submitted the information are significant, whilst the registered substance has already been tested in appropriate studies for irritation/corrosivity showing no remarkable skin or eye irritation. Thus, it is not possible to assume that the observed inhalation toxicity in the acute study is caused by a secondary corrosive effect. It is more probable that another systemic mechanism is causing the acute inhalation toxicity.

IV. 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 adapted to the technical progress by Commission Regulation (EC) No 761/2009 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.

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.

Done at Helsinki,

[redacted]

Jukka Malm
Director of Regulatory Affairs