~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: TPE-D-0000001517-74-06/F Helsinki, 10 November 2011

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

For 1,2,3-propanetricarboxylic acid, 2-hydroxy-, tri-c18-22 esters, EC No 700-316-5, 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 testing proposals set out in the registration dossier for **1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tri-C18-22 esters, EC No 700-316-5**, submitted by [redacted] ('Registrant'), latest submission number [redacted] for 100 - 1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX:

Annex IX, 8.6.2: Sub-chronic toxicity study (90 days) in rat by the oral route,

Annex IX, 8.7.2: Pre-natal developmental toxicity study in rat by the oral route.

The examination of the testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 11 October 2010.

ECHA opened a third party consultation for both testing proposals that was held from 11 January 2011 until 25 February 2011 and received some comments (see Section III below).

On 8 April 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 4 May 2011 the Registrant provided to ECHA comments on the draft decision requesting the extension of a deadline to submit an updated IUCLID dossier. ECHA reviewed the justification submitted and amended the draft decision by extending the deadline to submit an updated IUCLID dossier to 24 months from the date of the decision to provide the Registrant with reasonable time to comply with the requests.

On 17 June 2011 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. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 20 July 2011 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 did not modify the draft decision.

On 1 August 2011 the draft decision was referred to the Member State Committee.

On 1 August 2011 the Registrant provided comments on the proposals for amendment.

The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 20-23 September 2011, the Member State Committee modified the draft decision and a unanimous agreement of the Member State Committee on the modified draft decision was reached on 21 September 2011.

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.

II. Testing required

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

- Sub-chronic toxicity study (90 days) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route
- Pre-natal developmental toxicity study (Annex IX, 8.7.2, EU Method B.31) in rat by the oral route

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by 10 November 2013 an update of the registration dossier containing the information required by this decision.

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

Sub-chronic toxicity studies (90 day) (8.6.2) and pre-natal developmental toxicity studies (8.7.2) are part of the information requirements as laid down in Annex IX of the REACH Regulation. As the information on these two endpoints is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements, it follows that there is an information gap and that it is necessary to generate the data for these two endpoints using the test methods indicated in section II above (both of which include the possibility to consider a limit test).
The third party information received during the public consultation was evaluated in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoint, which would remove the need to perform vertebrate testing.

1. Use of results of the existing 28-day sub-chronic toxicity study (OECD Guideline 407), physico-chemical characteristics and chronic data availability before a sub-chronic 90-day toxicity study or a developmental toxicity study is conducted:

Toxicological activity and systemic absorption: The third party states that there is no evidence of toxicity in the 28-days study and no clear evidence of absorption (absence of any toxicological activity in acute, local irritation, sensitisation, repeated and chronic studies) on 2-hydroxypropane-1,2,3-tricarboxylic acid, tri (hexyl, octyl, decyl) ester, the chemical proposed by the Registrant as a read across chemical. The third party indicates that according to Annex IX, Column 2, Section 8.6.2, the sub-chronic toxicity study (90 days) does not need 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.

However, the Registrant has not proposed to adapt the information requirement on this basis. Furthermore, in the IUCLID dossier absorption was shown to occur and the Registrant did not provide data on human exposure. The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day study under column 2 of Annex 8.6.2. Therefore, the third party proposal does not provide a sufficient basis on which to reject the proposed test.

Available chronic study: The third party proposes read-across to tristearyl citrate, for which a chronic study in rats (2 years) is cited in a toxicological text book (Patty's Industrial Hygiene and Toxicology, John Wiley & Sons, Inc, 1981-1982). According to Annex IX, Column 2, Section 8.6.2, the sub-chronic toxicity study (90 days) does not need to be conducted if a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used.
The study cited by the third party cannot be evaluated by ECHA as insufficient information is provided in this secondary citation. However, to adapt the requirement for a 90-day repeated dose toxicity study for the registered

substance on the basis of read-across, similarity of the substances has to be adequately justified. Furthermore, to use the study cited by the third party, this study would need to meet the requirements in Annex XI, 1.1.2. and 1.5: adequate for the purpose of classification and labelling and/or risk assessment; adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3); exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and adequate and reliable documentation of the applied method.

Use of assessment factors: The third party proposes to use an assessment factor of 3 to extrapolate the 28-day NOAEL to derive a 90-day NOAEL.
There is neither such a specific rule for adaptation of the information requirement for a 90-day study under column 2 of Annex 8.6.2 nor a general rule under Annex XI of the REACH Regulation. Therefore, the third party proposal does not provide a sufficient basis on which to reject the proposed test.

2. Evaluation of human data on toxicity from acute exposure (TOXNET database) to the read-across substance tristearyl citrate before a sub-chronic 90-day toxicity study or a developmental toxicity study is conducted.

The third party proposes read-across to tristearyl citrate, for which a database on acute human exposure is available.
The information provided by the third party does not meet the requirements of Annex XI, 1.1.2, 1.1.3 and 1.5. Specifically, acute human data are not adequate to cover sub-chronic toxicity since exposure duration is not comparable. Therefore, this information does not provide a sufficient basis on which to reject the proposed test.

3. Use of *in vitro* (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential before a developmental toxicity study is conducted.

Scientifically validated *in vitro* methods such as the embryonic stem cell test, the limb bud micromass culture and the whole embryo culture may provide additional information which can be assessed together with existing *in vivo* data in a weight of evidence approach. However ECHA notes that the mentioned *in vitro* tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by the *in vivo* pre-natal developmental toxicity tests and therefore cannot be used as stand alone replacements tests. Furthermore these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination. ECHA notes that it is the Registrant's responsibility to establish the weight of evidence justification which demonstrates that any such data as may be obtained from the conduct of the proposed tests would be sufficient to meet the information requirements when submitting and/or updating its registration dossier.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of *in vitro* methods set out in Annex XI, Section 1.4. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

In conclusion, the information provided by third parties does not provide a sufficient basis on which to adapt the information requirement for a 90-day sub-chronic toxicity study or for a pre-natal developmental toxicity study.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out a sub-chronic toxicity study (90 days) and a pre-natal developmental toxicity study to meet the information requirements (Annex IX, 8.6.2 and 8.7.2, respectively).

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 as adapted to the technical progress 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 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.

Done at Helsinki,

[redacted]

Jukka Malm
Director of Regulatory Affairs