EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001815-72-05/F

Helsinki, 4 May 2012

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

For Isooctyl acrylate, CAS No 29590-42-9 (EC No 249-707-8), 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 Isooctyl acrylate, CAS No 29590-42-9 (EC No 249-707-8) submitted by [redacted] (Registrant), latest submission number [redacted] for above 1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(e) 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 X:

Annex IX, 8.6.2: Sub-chronic toxicity study (90 days) by oral route in rodents
Annex X, 8.7.3. Two-generation reproductive study

The present decision relates solely to the examination of the testing proposal for the sub-chronic toxicity study (90-day). The testing proposal for a two-generation reproductive toxicity study is addressed in a separate decision although both testing proposals were initially addressed together in the same draft decision.

The examination of the testing proposals was initiated on 5 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 March 2011 until 29 April 2011. ECHA received comments from third parties concerning the use of existing chronic study and 28-day repeated dose toxicity study, existing data on reproductive toxicity, the use of TTC (Threshold of Toxicological Concern) concept and on read-across from data for 2-ethylhexyl acrylate as part of the Acrylates Category. More information is provided in the section III, statement of reasons below.

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40 of REACH.

On 25 August 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.

The Registrant did not provide to ECHA any comments on the draft decision.

On 4 November 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 8 December 2011 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 those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and modified the draft decision.

On 19 December 2011, the draft decision was referred to the Member State Committee.

On 20 December 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 6-10 February 2012, the draft decision was split into two draft decision documents, one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposal for a repeated dose 90-day oral toxicity study in rodents.

The Member State Committee further modified the draft decision and a unanimous agreement of the Member State Committee on the draft decision relating to the testing proposal for a repeated dose 90-day oral toxicity study in rodents was reached on 9 February 2012.

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)(b) of the REACH Regulation, the Registrant shall carry out the following test using the indicated test method and the registered substance concerned by the present decision:

a. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route, modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin nephropathy.

The Registrant is reminded that based on the outcome of the toxicity tests, the Registrant may need to perform another pre-natal developmental study on a second species (REACH Annex IX 8.7.2., second column, and Annex X, 8.7.2). If the Registrant considers that such other pre-natal developmental study necessary, he should send the proposal for this testing to ECHA.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **4 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 concerned by the present decision and scientific information submitted by third parties.

a. Sub-chronic toxicity study (90-day)

A sub-chronic toxicity study (90-day) is a standard information requirement of Annex IX, 8.6.2 at the present tonnage level. ECHA notes that this standard information is not available in the present registration dossier. For the reasons set out below ECHA has decided to accept the testing proposal of the Registrant subject to conditions.

1) Analysis of third party comments

ECHA has examined the information submitted by third parties: [redacted] and [redacted], as follows:

[redacted]

Before a sub-chronic toxicity study (90-day, OECD Guideline 408) and a two-generation reproductive toxicity study (OECD Guideline 416) are conducted, consideration should be given to the following alternative testing strategies:

1.a) No need for 90-day testing (OECD 408) due to chronic toxicity data availability

The third party proposes that as stated under REACH Annex IX, Column 2, Section 8.6.2, the sub-chronic toxicity study (90 days) does not need to be conducted. A carcinogenicity assay through dermal route of exposure on mice is available (IUCLID dossier, Section 7.7).

However, the robust study summary of the chronic study in mice reveals numerous shortcomings (non-guideline study, inadequate description and justification of the method and dosing regime, inadequate reporting of the study results), and the study cannot be considered reliable. Since a reliable chronic study is not available, this is an insufficient basis upon which to reject the Registrant's testing proposal.

1.b) Clarification on 28-day repeated dose study (OECD Guideline 407) from 2010

The third party proposes that ECHA should ask the Registrant to provide clarifications on the 28-day repeated dose toxicity study (OECD 407) from 2010 that is included in the IUCLID dossier.

This is not valid information or studies that address the relevant endpoint and substance for the purpose of testing proposal evaluation. The Registrant was entitled to carry out a 28 day study without a testing proposal.

1.c) Exposure considerations: use the TTC for repeated dose end point

The third party proposes to use the TTC concept in order to evaluate if exposure is

negligible.

However, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, based on the exposure assessment carried out by the Registrant the conditions in Annex XI, Section 3.2 (a) (i) "absence or no significant exposure" are not met for worker exposures.

2. [redacted] Read-across from the data of 2-ethylhexyl acrylate

The third party proposed to see the REACH registration dossier for 2-ethylhexyl acrylate (CAS 103-11-7) as part of the Acrylates Category. There are 90-day studies available that may be suitable for read across.

A requirement of Annex XI, 1.5, is that the human health effects (of the registered substance) may be predicted from data on reference substances. There seem to be substantial differences between the known toxicology of the reference substance (2-ethylhexyl acrylate) and the registered substance.

For repeat-dose toxicity, in a 28-day oral rat study, the registered substance shows local (stomach) hyperplasia, renal hyaline droplets, liver growth, changed cholesterol, thyroid hyperplasia and no effect on serum transaminases/ Alkaline phosphatase or on body weights. By contrast, in a 90-day inhalation study in rat, the 2-ethylhexyl acrylate shows local (nasal) irritation, fatty liver, effect on serum transaminases and alkaline phosphatase, decreased body weight gain, no renal effects, no thyroid effects.

For prenatal developmental toxicity, a limit dose oral rat study shows that the registered substance yields an increased incidence of visceral and/or skeletal variants, at a dose which is maternally toxic. The dose-response relationship is uncharacterised. In a rat inhalation study, the 2-ethylhexyl acrylate shows no effects at maternally toxic doses.

Further, 2-ethylhexyl acrylate is a skin sensitizer but the registered substance is not.

Thus there are multiple differences in multiple endpoints in the toxicity of the two substances. Consequently, it is not possible to predict the human health effects of the registered substance from data on the reference substance, and this requirement of Annex XI, 1.5, is not met. In addition, there is not sufficient adequate information to justify the addition of the registered substance to the acrylate category, which is a requirement of Annex XI, 1.5.

The available information does not give adequate basis to read across from 2-ethylhexyl acrylate, since the information submitted by the third party does not meet the conditions for the adaptation on the basis of read-across (Annex XI, Section 1.5). Therefore, it cannot constitute an acceptable adaptation to standard information requirements, and it is therefore an insufficient basis upon which to reject the Registrant's testing proposal.

2) Analysis of information in the registration dossier

The dossier contains a 28-day rat study by oral route. The findings include hyaline droplet formation in the kidneys of the 300 and 1000 mg/kg-day-treated male rats. The Registrant considers this result attributed to the male rat-specific alpha-2u-globulin protein and that it

is not relevant for risk assessment in humans. However, ECHA considers that there is insufficient data provided to justify the Registrant's assertion that alpha-2u-globulin has mediated the kidney toxicity.

The test for sub-chronic (90-day) toxicity as proposed by the Registrant is necessary to fulfil the information requirement of section 8.6.2 of Annex IX to the REACH Regulation. ECHA decided to modify the Registrant's testing proposal by including urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD 408, section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin nephropathy.

3) Conclusion

Pursuant to Article 40(3)(b) ECHA may take a decision requiring the Registrant to carry out the proposed test, but modifying the conditions under which the test is to be carried out.

Accordingly, pursuant to that Article the Registrant is requested to provide information on the Annex IX, 8.6.2 endpoint by carrying out a sub-chronic toxicity study (90-day) in rat by the oral route by using EU Method B.26, modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin nephropathy.

b. Deadline for submitting the requested information

In the draft decisions 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 requested a 2-generation reproductive toxicity study. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 18 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

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in the dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed tests, 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 the joint registrants of the same substance to agree with the tests proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant.

Finally, the studies must be shared by the joint registrants concerned.

V. 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 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.

VI. 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.

[redacted]

Jukka Malm
Director of Regulatory Affairs