ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114303247-59-01/F Helsinki, 30 July 2015

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

For Fatty acids, C6-24 and C6-24-unsatd., Me esters, distn. Residues, CAS No 102242-52-4 (EC No 310-083-8), registration number: [redacted]

Addressee: [redacted]

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for Fatty acids, C6-24 and C6-24-unsatd., Me esters, distn. Residues, CAS No 102242-52-4 (EC No 310-083-8), submitted by [redacted] (Registrant).

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). The scope of this compliance check is limited to the standard information requirement of Annex VIII, Sections 8.4.3. Annex IX, Section 8.7.2, and Annex X, Section 8.7.3 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+T per year. This decision does not take into account any updates submitted after 05 March 2015, 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 4 April 2013.

On 27 September 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt fo the draft decision.

On 30 October 2013 ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex VIII, IX and X, Sections 8.4.3, 8.7.2. and 8.7.3. The compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) was removed from the draft decision due to the legislative amendments to the REACH Regulation regarding Annex IX/X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning the information requirement of Annex X, Section 8.7.3. However, ECHA Secretariat did consider further the Registrant's comments concerning the information requirements of Annex VIII and IX, Sections 8.4.3 and 8.7.2. On the basis of this information and change of scope, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 5 March 2015 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

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

1. *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17/OECD 476);

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

B. Deadline for submitting the required information

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 **08 August 2016**.

Notes for consideration by the Registrant:

In light of the comments made by the Registrant, ECHA points out that the Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VIII 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 sound 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 Authorities of the Member States for enforcement.

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 VIII to X of the REACH Regulation.

1. Mutagenicity, *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.)

In accordance with Articles 10(a)(vii), 12(1)(e) and with Annex VIII, section 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1 and Annex VIII, section 8.4.2. The registration dossier reports negative results for the both *in vitro* studies. Therefore the REACH Regulation requires that information on *in vitro* gene mutation in mammalian cells (Annex VIII, 8.4.3.) is provided in the dossier. ECHA notes furthermore that a cytogenicity study (be it *in vitro* or *in vivo*) cannot be used for *in vitro* or *in vivo* mammalian cell gene mutation information requirements. Cytogenicity studies and gene mutation studies are two distinct mechanisms of genotoxicity: cytogenicity studies detect structural and numerical chromosome aberrations whereas gene mutation studies detect gene or point mutations. ECHA concludes that the Registrant has neither provided this standard information nor adapted the requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In its comments to the draft decision the Registrant has proposed to update the dossier with studies regarded as Weight of Evidence for information requirement of Annex VIII 8.4.3. *in vitro* gene mutation study in mammalian cells. The Registrant further clarified that the intention to provide such weight of evidence data is "based on the justification for structurally related substances." ECHA acknowledges the Registrant's comment. However, in absence of any supporting data or adaptation justification for the given endpoint (mutagenicity) in the IUCLID dossier, ECHA has decided not to amend the draft decision, as it is not possible for ECHA to assess the adequacy of the adaptation argument.

Therefore, pursuant to Article 41(1)(a) 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: *In vitro* mammalian cell gene mutation test (test method: EU B.17./OECD 476).

2. 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.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2. Instead, the Registrant has proposed to adapt the information requirement of prenatal developmental toxicity study. The Registrant has justified the proposal for adaptation with reference to low toxicological activity, toxicokinetic data and no or no significant human exposure, without specifying the adequate adaptation possibility given in the respective column 2 of that section of Annex IX.

According to Annex IX, 8.7., Column 2, third indent, (and Annex X, Section 8.7, third intend), the study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*"

The Registrant has however not adequately documented that the conditions of that adaptation possibility are fulfilled. While the registrant has provided some evidence of low toxicity, it has not been documented that there is "no systemic absorption via relevant routes". On the contrary, according to Section 7.1. of IUCLID, the substance is bioavailable. Moreover, according to the process descriptors provided by the Registrant, there is potential for human exposure.

Therefore, since the Registrant has not provided sufficient information to show that conditions of the daptation in Column 2 of Annex IX, 8.7 are met, the adaptation of the information requirement proposed by the Registrant cannot be accepted.

Read-across

In his comments to the draft decision, the Registrant has proposed to adapt the information requirement for a pre-natal developmental toxicity study and referred to read-across from 2-Ethylhexyl Stearate, for which a pre-natal developmental toxicity study has been published [redacted]. In addition, other source substances (Methyl Oleate, Palmitate Methyl Esters, Ethyl Oleate and Butyl Stearate) have been suggested for the read-across, but for these substances, no pre-natal developmental toxicity study has been provided. ECHA thus assessed the provided information in the light of the criteria of Annex XI, Section 1.5 of the REACH Regulation.

Structural similarity
ECHA points out that the first prerequisite of the read-across, pursuant to Annex XI, Section 1.5 of the REACH Regulation is structural similarity between the source and the target substance of the read-across. While it is recognized that "Fatty acids, C6-24 and C6-24-unsatd., Me esters" (i.e. the main component of the registered substance) and 2-Ethylhexyl Stearate may have some structural similarities, the registered substance is a mixture of several components, i.e. glycerides, polymers, free fatty acids, and methanol. The Registrant has not explained in his comment, how these other constituents can be covered by the read-across. Data on the concentration and on the toxicity of these constituents has not been provided, and therefore it is not possible to assess, whether read-across can cover these other constituents. Finally, the Registrant has described two manufacturing processes. The residues produced by means of these two processes differ markedly in composition, in particular the proportion between glycerides and free fatty acids.

The main component of the registered substance contains an ester functionality and the only substance with adequate data on pre-natal developmental toxicity is a stearate (i.e. contains a carbonic acid functionality) and therefore they are structurally different. The relevance of the data of the source substance for the prediction of the property of the target substance has not been assessed.

Therefore, ECHA considers that the first prerequisite of the read-across, i.e. structural similarity has not been demonstrated.

Boundaries and membership in the chemical group
In his comment, the Registrant has provided a matrix, which gives some relevant information on 2-Ethylhexyl Stearate, Methyl Oleate, Ethyl Oleate and Butyl Stearate. However, the registered substances has not been included in that matrix. Furthermore, the Registrant has not provided an explicit definition of the substances, which belong to the group for the purpose of read-across and there is no explanation how the registered substance (considering all its constituests) fits within the boundaries of the grouping as intended.

Documentation
The Registrant has referred to four studies on different source substances for his read-across, two were made with "stearates" and three other "related compounds" and two were made using esters. While there may be some relevant structural similarity and some limited data on low systemic toxicity on the substances, the Registrant has not explained the relevance of the information generated with the given source substances for the target substance subject to this decision.

Additionally, the Registrant has not provided a study record for any of these studies thus not fulfilling the requirement to provide adequate and reliable documentation, as requested in Annex XI, Section 1.5 of the REACH Regulation.

Toxicokinetics
Concerning the toxicokinetics of some of the group members, the Registrant has explained that "*Higher molecular weight aliphatic esters are readily hydrolysed to the corresponding alcohol and acid and then generally oxidised to carbon dioxide and water. In addition, there is data from human and animal studies that show rapid absorption in the liver and breakdown of the substance into methanol and fatty acids; there is absence of the substance itself in the plasma/blood and in the urine.*" While this information might be considered relevant, adequate and detailed comparison of the metabolism of the source(s) and target substance of the read-across is missing. As the Registrant's conclusions are inadequately supported and documented, ECHA cannot verify whether the information supports their predicition.

The proportion of the short chain length fatty (e.g. C-6) acids in the registered substance is not reported. That is a significant gap, because the bioavailability and toxicity of these constituents may deviate significantly from that of the longer chain length fatty acids (e.g. C-24) and of 2-Ethylhexyl Stearate.

Overall, the Registrant did not provide sufficient data on common precursors and/or breakdown products that the members of this chemical group have (Annex XI, Section 1.5 of the REACH Regulation).

Prediction of the effects
The Registrant did not explain how human health effects of the registered substance (target substance) can be predicted from the reference (source) substances of the group. The Registrant did not explain the mechanistic basis, i.e. failed to provide a read-across hypothesis.

The weakness of the toxicokinetic data specified above adds to the uncertainly of predicting the hazardous properties of the registered substance.

ECHA notes that there is also a concern on whether the selection of the source substances of the read-across has been appropriate. More notably, the source substances consist of C12, C14, C16 and C18 substances, while the range covered by the registered substance starts at C6. Thus, the lighter fatty-acids are not at all represented among the source substances, while they may be the most relevant ones for the read-across, which is a particular concern. The possibility of prediction of the effects of the registered substances is impaired, because one constituent of it, i.e. C-6 substances is likely to be more bioavailable than the other fatty acids.

In summary, ECHA considers it cannot verify from the information provided that the differences in structures do not cause any difference in properties or whether the read-across is valid for the endpoint and hence the criterion of predictability of human health and environmental effects of the target substance is not fulfilled, as required under Annex XI, Section 1.5 REACH.

Weight of Evidence

In the comments the registrant has also proposed a Weight of Evidence and proposes that the WoE consists of the following cumulative sources of confirmation:

- "The substance is of low toxicological activity.
- The metabolism of the substance does not lead to reprotoxic metabolites.
- Evidence from chronic toxicity studies.
- Evidence from reproductive toxicity studies."

ECHA finds that the reproductive toxicity parameters covered in a pre-natal developmental toxicity study have either not been sufficiently covered in studies that have been provided and/or depend on a read-across that has been found insufficiently documented and justified, as already specified above. Therefore, the cumulative evidence provided by these studies does not correspond with the specific REACH information requirement set in Annex X, column 2 nor satisfy the criteria of the weight of evidence adaptation as described in Annex XI, Section 1.2 REACH.

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)(a) and (b) 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 the conditions for these adaptations are not fulfilled, 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 the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2. of the REACH Regulation.

3. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 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 two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.). As Annex X, Section 8.7.3. is not addressed in the present decision, ECHA Secretariat considers that a reasonable time period for providing the required information in the form of an updated IUCLID dossier 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Leena Ylä-Mononen, Director of Evaluation

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.