ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000005287-69-02/F Helsinki, 17 September 2014

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

For allyl heptanoate, CAS No 142-19-8 (EC No 205-527-1), 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 for allyl heptanoate, CAS No 142-19-8 (EC No 205-527-1), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex IX, Sections 8.6.2. and 8.7.2. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates submitted after 12 June 2014, 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.

The compliance check was initiated on 6 March 2013.

On 4 June 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted]

On 1 July 2013 ECHA received comments from the Registrant. On 8 July 2013 the Registrant updated his registration dossier (submission number [redacted]). The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 2014 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

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(d), 13 and Annex IX, 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. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408); and
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU 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 registration to ECHA by **26 September 2016**. The timeline has been set to allow for sequential testing as appropriate.

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.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI 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 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 Enforcement Authorities of the Member States.

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 requirement.

The Registrant has provided comments to the draft decision and has updated the registration.

The Registrant indicated in his comments that the substance is used as an ingredient in cosmetic products. The Registrant indicated further that the requirement to conduct the studies within this decision shall be postponed until the consequences ("marketing ban") of conducting animal studies for REACH purposes of ingredients used in cosmetic products has been clarified by ECHA and the Commission.

ECHA notes that in its Communication of March 2013 the European Commission clearly indicated that "*animal testing that has clearly been motivated by compliance with non-cosmetics related legislative frameworks should not be considered to have been carried out 'in order to meet the requirements of this Directive/Regulation'. The resulting animal testing*

data should not trigger the marketing ban and could subsequently be relied on in the cosmetics safety assessment" (Communication on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics, 11.3.2013, COM(2013) 135 final). This means the following:

(i) Registrants of substances that are exclusively used in cosmetics may not perform animal testing in order to meet the information requirements of the REACH human health endpoints, with the exception of any testing required for the purpose of assessing the risks arising from exposure to workers.
(ii) Registrants of substances that use the substance also for non-cosmetic uses (i.e. mixed-use substances) are permitted to perform animal testing, as a last resort, for all human health end-points.
(iii) All registrants (whether or not they only use the substance for cosmetic purposes) are permitted to perform animal testing, as a last resort, for all environmental endpoints.

In this case since the registered substance is used for cosmetic as well as for non-cosmetic purposes the Registrant is permitted to perform animal testing for all human health endpoints. Such testing should not trigger the marketing ban in the Cosmetics Regulation.

In the updated registration, the Registrant has adapted the standard information requirements for the sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.) and the pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across adaptation following REACH Annex XI, Section 1.5. The read-across approach is reflected in the following section.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

The Registrant indicates that the substance subject to the present decision, allyl heptanoate (target substance), is rapidly transformed in allyl alcohol (source substance) and carboxylic acid via enzymatic hydrolysis of the ester by non-specific esterases in the gastrointestinal tract, the liver, or when absorbed through the skin. Also allyl hexanoate (another source substance) is metabolised to allyl alcohol in the same way and therefore considered as suitable read across substance. In summary, the Registrant assumes that both chemicals will have comparable modes of action with regard to systemic toxicity, allowing read-across for the covered endpoints:

- Acute oral toxicity (read across from allyl hexanoate)
- Acute inhalation toxicity (read across from allyl alcohol)

- Repeated dose toxicity: oral, feeding (read across from allyl hexanoate)
- Developmental toxicity (read across form allyl alcohol)
- One-generation reproductive toxicity (read across from allyl 3-cyclohexylpropionate).

b. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

For the endpoint sub-chronic toxicity (90-day) (Annex IX, Section 8.6.2.) the Registrant has provided results from a 1-year oral (feeding) study in rats with the source substance allyl hexanoate (Hagan et al. 1967) to fulfill the information requirement.

For the endpoint pre-natal developmental toxicity (Annex IX, Section 8.7.2.) the Registrant has referred to results from a pre-natal developmental toxicity study performed with the metabolite allyl alcohol from the ECHA database to fulfill the information requirement.

A read-across justification document was provided together with the comments on the draft decision and in the updated registration dossier (submission number [redacted]). In this read-across justification, the Registrant justifed the read-across with arguments that are summarised as follows:

(i) Enzymatic hydrolysis of allyl esters by unspecific esterases

The Registrant assumes rapid transformation of allyl esters to allyl alcohol by unspecific esterases. The Registrant has provided general information on hydrolysis by esterases in different tissues.

(ii) Allyl alcohol toxicity

The Registrant indicated that allyl alcohol, one cleavage product of allyl heptanoate, is rapidly converted in the liver to acrolein by hepatic alcohol dehydrogenase. Acrolein may then be further oxidized to acrylic acid, or to glycidaldehyde with subsequent conversion to glyceraldehyde by an epoxide hydrolase. The Registrant indicated that, alternatively, acrolein may react directly with glutathione or other low molecular weight thiol compounds. Glutathione conjugation is considered a major route of acrolein detoxification *in vivo*.

(iii) Carboxylic acid toxicity

The Registrant explained that the other cleavage products of allyl hexanoate or allyl heptanoate are hexanoic or heptanoic acid, respectively, which undergo complete metabolism via the fatty acid b-oxidation pathway. Therefore, the Registrant considers the heptanoic acid part of allyl heptanoate of negligible toxicological relevance.

c. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

ECHA notes the following:

(i) Enzymatic hydrolysis of allyl esters by unspecific esterases

ECHA understands that the proposal by the Registrant to read-across from a 1-year oral (feeding) toxicity study in rats using allyl hexanoate (source substance) to allyl heptanoate (target substance and registered substance) and to read-across from a pre-natal developmental toxicity study with allyl alcohol (source substance) to allyl heptanoate (target

substance and registered substance) is based on a postulated rapid hydrolysis of allyl heptanoate and allyl hexanoate to the carboxylic acids and to allyl alcohol.

ECHA notes that the Registrant did not substantiate that hydrolysis of allyl hexanoate or allyl heptanoate is rapid and complete; it is merely postulated on the basis of generic information without quantitative data on allyl heptanoate and allyl hexanoate.

In contrast, ECHA observes that the assumption of a rapid hydrolysis of allyl heptanoate or allyl hexanoate to allyl alcohol is not supported by the availabe data. In the 90-day study with allyl alcohol mainly local toxicity in the forestomach was observed (≥6 mg/kg bw/d). Assuming a rapid hydrolysis of allyl heptanoate or allyl hexanoate, also local effects in the gastrointestinal tract would have been expected as a consequence of allyl alcohol formation. However, no local effects in the gastrointestinal tract were observed with allyl heptanoate up to 100 mg/kg bw/d and with allyl hexanoate up to 214 mg/kg bw/d.

(ii) Allyl alcohol toxicity

ECHA notes that allyl heptanoate and allyl alcohol do not have a common functional group and differ in their toxicological profiles.

ECHA notes that read-across from allyl alcohol to allyl heptanoate for pre-natal developmental toxicity is impaired (i) by the obviously non rapid hydrolysis of allyl heptanoate in the gastrointestinal tract as indicated above but its hydrolysis to allyl alcohol and further metabolites in the liver (ii) the local toxicity of allyl alcohol in the gastrointestinal tract. Due to the irritating property of allyl alcohol to the forestomach (≥6 mg/kg bw/d) leading to maternal and offspring mortality (35 mg/kg bw/d), dosing with allyl alcohol is limited. However, with allyl heptanoate higher dosing (up to 100 mg/kg bw/d) without local irritation to the forestomach can be achieved to evaluate the hazard of allyl heptanoate for pre-natal developmental toxicity. Therefore, a pre-natal developmental toxicity study with allyl alcohol is not sufficient to address pre-natal toxicity of allyl heptanoate to a sufficient extent.

(iii) Carboxylic acid toxicity

ECHA notes that the Registrant did not provide any substance-specific information to support the assumption that the hydrolysis products of allyl heptanoate and allyl hexanoate, hexanoic and heptanoic acid, are of negligible toxicological relevance and will not differ with respect to sub-chronic toxicity.

d. ECHA analysis of the endpoint-specific read-across approach in light of the requirements of Annex XI, 1.5.

(i) Sub-chronic toxicity (90 days)

To cover the information requirement for a sub-chronic toxicity study (90 days), the Registrant has provided a 1-year oral (feeding) study in rats with the source substance allyl hexanoate (Hagan et al. 1967). However, this study is a pre-GLP study with several shortcomings. For example, the study was performed with only 10 instead of 20 animals per dose group as indicated in the test method (EU B.16/OECD 408). Furthermore, the animals were exposed to allyl hexanoate at only one dose level via the diet (214 mg/kg b/d) that did not lead to any toxicological effect with no higher doses tested. Hence, key parameters of the sub-chronic toxicity study (90-day) are not met and this study cannot be used to cover the information requirement for a sub-chronic toxicity study (90-day).

Furthermore, ECHA understands that the Registrant postulates that both substances allyl hexanoate and allyl heptanoate will have the same effects because the toxicity of the two carboxylic acids can be regarded insignificant, which leaves only the allyl alcohol as the substance that determines the toxicity of both. However, ECHA notes that, based on the available information provided, allyl heptanoate and allyl hexanoate may differ in their toxicity profile. Whereas no toxicity was reported with allyl hexanoate in the 1-year oral toxicity study up to 214 mg/kg bw/d, liver toxicity was the main finding with allyl heptanoate administered via gavage in an OECD 421 screening study at 30 mg/kg bw/d and in a short-term repeated dose toxicity study (28-day) at 100 mg/kg bw/d. The Registrant justified the differences in toxicity with different types of oral administration (gavage with allyl heptanoate and feeding with allyl hexanoate). However, the Registrant did not support this assumption by other information. Consequently, the toxicological properties of the substances may not be similar and a prediction of properties between the substances is not possible.

(ii) Pre-natal developmental toxicity

As indicated above, read-across from allyl alcohol to allyl heptanoate for pre-natal developmental toxicity is impaired by the local toxicity of allyl alcohol in the gastrointestinal tract. Furthermore, the Registrant did not substantiate that hydrolysis of allyl heptanoate to allyl alcohol is rapid and complete. In contrast, the available data indicate that hydrolysis of allyl heptanoate may not be rapid and complete in the gastointestinal tract leading to a different toxicity profile for allyl acohol compared to allyl heptanoate after oral administration. Consequently, the toxicological properties of the substances are not likley to be similar and a prediction of properties between the substances is not possible.

In the read-across approach for this endpoint, the Registrant tried to address only the toxicity of the metabolite allyl heptanoate. However, the Registrant did not document or demonstrate that the parent compound allyl heptanoate or the other metabolite, heptanoic acid, will not show a hazard for pre-natal developmental toxicity.

e. Conclusion on the read-across approach

ECHA concludes that the read-across approach for sub-chronic toxicity (90-days) does not fulfil the criteria of Annex XI, Section 1.5. and cannot be accepted because the provided one-year study does not adequately and reliably cover key parameters for a sub-chronic toxicity study (90 days) and the substances used for read-across (read across from allyl alcohol to allyl heptanoate) may not be toxicological similar.

ECHA concludes that the read-across approach for pre-natal developmental toxicity does also not fulfil the criteria of Annex XI, Section 1.5. and cannot be accepted because the substances used for read-across (read across from allyl hexanoate to allyl heptanoate) have different functional groups and are not likely to be toxicological similar. Furthermore, the Registrant did not address the pre-natal developmental toxicity of the other hydrolysis product heptanoic acid.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements in the technical dossier, based on the read-across substances, does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, section 8.6.2. 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.

In the technical dossier the Registrant provided information with which he initially sought to fulfil this standard information requirement. The provided information stems from a "28-day subchronic oral toxicity study" (test method: OECD 407). However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days.

In the comments to the draft decision and in the updated registration dossier, the Registrant has adapted the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concluded that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above).

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In light of the properties of the substance (liquid with low vapour pressure not irritating to the skin) and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate. According to the test method the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit information on sub-chronic toxicity (90-day) in rats, oral route (test method: EU B.26./OECD 408) derived with the registered substance subject to the present decision.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

A pre-natal developmental toxicity study 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.

In the comments to the draft decision and in the updated registration dossier, the Registrant has adapted the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concluded that the substances are not likely to be similar as required in Annex XI, 1.5. (see Section III, 0. above).

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirements. 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) and 41(3) of the REACH Regulation, the Registrant is requested to submit information on Pre-natal developmental toxicity on rats or rabbits, oral route (test method EU B.31/OECD 414) on the registered substance.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted 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 to ensure that his registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In carrying out the studies required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, 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://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]
Leena Ylä-Mononen
Director of Evaluation