Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482409-39-01/F
Substance name: Alcohols, C9-11-branched
EC number: 271-360-6
CAS number: 68551-08-6
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 31 July 2018

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114342397-45-01/F of 14 October 2016 ("the original decision") ECHA requested you to submit information by 21 June 2018 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information

Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[1].

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA

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Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[2] by Wim De Coen, Head of Unit, Hazard Assessment

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

Appendix 1: Reasons

This decision is necessary according to Article 42(1) of the REACH Regulation because in your updated registration as a response to the decision CCH-D-2114342397-45-01/F ("the compliance check decision") you have provided information that ECHA has assessed for compliance with the information requirements of the REACH Regulation and the outcome is that your registration still does not comply with the information requirements addressed in the compliance check decision.

0. Assessment of the read-across approach

Legal framework

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[3]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[4]: (1) (Bio)transformation to common compound(s) – the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s) – the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the adequacy and reliability of the studies which are to be read-across.

Information provided

In the compliance check decision you were requested to submit information derived with the registered substance (the target substance). In the updated registration subject to follow-up evaluation, you have applied a read-across approach based on grouping of substances (category approach) and provided experimental studies with analogue substances Branched alcohols, C7-9, C8 rich ([redacted], EC 271-231-4) and Alcohols, C11-14-iso-, C13-rich ([redacted], EC 271-235-6) (the source substances) and have provided category and read-across documentation.

You have proposed a category consisting of Alcohols C7-C9-iso, C8-rich [redacted] Alcohols C8-C10-iso, C9-rich [redacted], Alcohols C9-C11-iso, C10-rich (Exxal 10), Alcohols C9-C11-branched ([redacted] the registered substance), and Alcohols C11-c14-iso [redacted] The 90-day repeated dose toxicity study results provided with analogue substances were used to fill in the data for the registered substance (and other category members). To support the read-across, you submitted a read-across justification document [redacted]

Based on the information provided in your read-across justification document, ECHA understands that you consider that the members of your category "*are similar in molecular structure, physicochemical properties, use, and manufacturing processes*" and that "*Based on these unifying considerations and experimental data demonstrating biological effect at the high and low end of the variation in carbon backbone length, read across within this group is appropriate among these analogues*". You specify that the predictions will be made within this category from "*data from the source substance with a carbon backbone length closest to target substance*".

Evaluation of the adaptation

ECHA has assessed your adaptation in the light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and considers that the read-across cannot be accepted for the reasons presented below.

Annex XI, Section 1.5 of the REACH Regulation requires that "*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or*

[4] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

follow a regular pattern as a result of structural similarity may be considered as a group". According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008) "*a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved*". This aspect of particular importance in the context of your read-across approach as you indicated your intention to "*demonstrate biological effects at the high and low end of the variation in carbon backbone length*" and to use data from the source substance with a carbon backbone length closest to the target substance to predict the properties of the substances within the group.

You have reported information from toxicokinetic investigations and from sub-chronic (90-day) toxicity studies conducted with the substances located at the lower and at the higher end of the carbon backbone length of the category, i.e. [redacted] and [redacted], respectively.

Toxicokinetic properties

According to the information presented in your read-across justification document, the toxicokinetic properties of the members of your category may be affected by variations in the structure of these substances. Specifically, absorption decreases as the carbon chain length increases. The carbon chain length and the position, number and size of alkyl substituents on these carbon chains may affect the metabolic pathways involved in the detoxification of the substances. Unsaturation may also lead to the formation of different types of metabolites. The *in vivo* toxicokinetic studies conducted with [redacted] and [redacted] revealed differences in some toxicokinetic parameters between these two category members. Repeated oral administration of [redacted] at doses equal and greater than 450 mg/kg/d led to the saturation of the principal metabolic pathway. No such saturation was noted in a comparable study performed with [redacted]. The observation of these differences in toxicokinetic properties conflict with your expectation reported in the read-across justification document that "*oxo alcohols exhibit similar toxicokinetic and metabolism properties*".

Toxicological properties

Whilst the results from the sub-chronic studies reported in your technical dossier identified common target organs the findings also suggest that the toxicological profiles of [redacted] and [redacted] do differ to some extent. The sub-chronic studies conducted in rats via the oral route using both substances identified microscopic findings in the liver and the kidney in the mid and high dose groups. The hepatocellular hypertrophy was considered as non-adverse for both substances. The tubular degeneration, regeneration and the hyaline droplet accumulation observed in the kidneys were regarded as α-2-u-globulin mediated effects of no relevance to humans.

However, ECHA observes that additional findings reported in the study performed with [redacted] were not identified in the study conducted with [redacted]. Specifically, increased prevalence of thyroid follicular cell hypertrophy/hyperplasia was observed in males and females from the mid and high dose groups in the sub-chronic toxicity study conducted with [redacted]. You considered that these effects were non-adverse and may represent an "*adaptive response to* [redacted]*-related hepatic microsomal enzyme induction and associated*

thyroxine metabolism". No information on microsomal enzyme activity is provided to support this assumption.

In the absence of further detailed information on the microsomal enzyme activity in the robust study summary for that study, ECHA considers that the secondary nature of the thyroid findings is not established.

Furthermore, no similar microscopic findings in the thyroid glands were reported in the 90-day study performed with [redacted] whereas similar hepatotoxicity has been observed in that study. According to the information on toxicokinetic presented in the read-across justification document and mentioned above, the constituents of [redacted] are estimated to be more bioavailable than those of [redacted] due to their shorter carbon chain length. Evidence of saturation of the metabolic pathway has been provided for [redacted], suggesting prolonged systemic exposure to the constituents of [redacted] in their native form.

Taken together, and despite the adjustment of the test doses used to conduct these studies to accommodate for differences in toxicokinetic properties, these parameters suggest that [redacted] and [redacted] may have a different toxicological profile.

The ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.6.2, Section R.6.2.4.1 – step 6, (version 1.0, May 2008) stresses that "*if toxicity is expected to vary in a regular pattern from one end of the range of category members to the other end (e.g. high toxicity to low toxicity), samples chosen for testing should bracket both ends of toxicity. If the category is large, testing also needs to be performed and/or data should be available for one or more members in the middle of the range of toxicity*". You have provided information from sub-chronic toxicity studies conducted on [redacted] and [redacted], which are located at the lower and at the higher end of the carbon backbone length of the category, respectively. As indicated above, the information obtained from these studies suggest that these substances have different toxicokinetic and toxicological properties. No information on the properties of other category members after repeated administration is provided. In particular, no data obtained from a bridging study i.e. short term repeated exposure study and informing on the properties of the target substance [redacted] is currently available.

On that basis, ECHA considers that no regular pattern or trend of the properties across the category can be derived from the only two experimental studies currently available on the members located at the boundaries of the category. Therefore, in the absence of additional information, ECHA considers that the data obtained from these two sub-chronic repeated dose toxicity studies on the substances does not constitute an adequate basis to support your hypothesis whereby substances included in the category have the same type of biological effects or that their properties follow a trend.

Conclusion

For the reasons presented above and on the basis of the information provided in your registration dossier, ECHA considers that there is not sufficient support for your proposal that the target substance and the source substances have similar toxicological properties as a result of structural similarity, similarity in physicochemical properties and in manufacturing processes and similarity in biological effects among the category members. For this reason, ECHA considers that your hypothesis is not a reliable basis whereby the

properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group.

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

In the compliance check decision you were requested to submit information derived with the registered substance for Sub-chronic toxicity study (90-day), via oral route.

In the updated registration subject to follow-up evaluation, you have applied a read-across approach based on grouping of substances (category approach) and provided experimental studies according to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) with analogue substances Branched alcohols, C7-9, C8 rich ([redacted], EC 271-231-4) and Alcohols, C11-14-iso-, C13-rich ([redacted], EC 271-235-6) and category and read-across documentation.

ECHA considers that the read-across cannot be accepted for the reasons outlined above.

In your comments to the draft decision, you have indicated that additional information will be generated to strengthen the read-across for this grouping of alcohols. In addition, you acknowledge that further studies are needed to confirm the similarities and hypothesis used, therefore you have agreed to perform the requested sub-chronic toxicity study.

As detailed above, the request in the original decision was not met, and you are still required to provide information on Sub-chronic toxicity study (90-day), via oral route (Annex IX, Section 8.6.2); test method: EU B.26/OECD TG 408 with the registered substance.

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114342397-45-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

In your comments you agreed to provide the requested study. You also requested ECHA to put the decision making on hold, until the results of the requested study becomes available. However, ECHA cannot accept the request for several reasons. Firstly, according to the procedure laid out in Article 50(1), the Agency shall inform the competent authorities of the submission of the comments without delay. Secondly, for the principle of equal treatment towards other registrants. In addition, this decision is the outcome of the follow-up assessment to the original ECHA decision that established the deadline by when you were to bring your dossier into compliance with the information requirement. Therefore, no additional time can be granted by ECHA.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.