EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 30 June 2020

Addressee: [redacted]

Decision number: CCH-D-2114512482-58-01/F
Substance name: Esterification products of 1,3-dioxo-2-benzofuran-5-carboxylic acid with nonan-1-ol (the Substance)
EC number: 941-303-6
CAS number: -
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 3 January 2019

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

By decision CCH-D-2114382253-51-01/F of 18 December 2017 ("the original decision") ECHA requested you to submit information by 3 January 2019 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 requirement:

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

You are therefore still required to provide the information requested in the original decision.

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

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.

Approved[2] under the authority of Christel Schilliger-Musset, Director of 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-2114382253-51-01/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

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. 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 (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4],[5].

Information provided

In the compliance check decision you were requested to submit information derived with the registered substance "TM9" (the Substance). In the updated registration subject to follow-up evaluation, you have applied read-across approach based on analogue approach where hypothesis is based on different compounds which have the same type of effect(s) (RAAF scenario 2). You have provided experimental studies with the source substances 1,2,4-benzenetricarboxylic acid, trioctyl ester; trioctyl benzene-1,2,4-tricarboxylate ("TM8") (EC 201-877-4), tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate ("TM8-10") (EC 290-754-9), Tris (2-ethylhexyl) 1,2,4-benzenetricarboxylate ("TOTM") (EC 220-020-0) and have provided read-across justification documentation.

You consider in your read-across justification documentation that "*because of the similarity in chemical structure and common degradation – hydrolysis to the di-ester, then mono-ester then further hydrolysis to yield trimellitic acid and the corresponding alcohol – it is considered that the (eco)toxicological properties of the substances in this category will be similar*".

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.

---

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". Within this documentation "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of your Substance can be predicted from the data on the source substance(s).

As indicated above, your read-across hypothesis is based on the on different compounds which have the same type of effect(s). In this context it is important consider that there is adequate evidence to support the hypothesis. The documentation of your adaptation must include information to assess the impact of exposure to non-common compounds. Relevant, reliable and adequate information allowing to compare the properties of the Substance and source substance is necessary to assess the impact of exposure to all the constituents of the Substance and source substance on their toxicological properties. Information on toxicological properties can be obtained, for example, from bridging studies of comparable design and duration for your Substance and the source substances.

In the technical dossier, you have provided experimental data on the source substances, toxicokinetic data on the source substance "TOTM", *in silico* predictions of ADME profiles for the Substance and source substances.

In your read-across justification document you identify the following issues:

"In the present read-across study, an overall medium uncertainty was associated with similarity justification. However, the following issue was highlighted: "i) the endpoint to read-across does not have yet well-defined mechanistic bases (high-tier endpoint, ii) ADME assessment was mainly based on simulated data; iii) identification of potential metabolites and related structural and mechanistic profiles was mainly based on in silico predictions iv) a metabolite related to hepatotoxicity was identified for the target but not for the source compounds.. The main uncertainties associated with the read-across argument were related to the following issues: i) endpoint-type, ii) no bridging studies among the source and target substances."

In your comments to the draft decision, you elaborated on the anticipated concentrations of constituents leading to the formation of the metabolites giving rise to the alerts for liver toxicity based on the composition of the Substance. On that basis you assessed the impact of the potential presence of these metabolites on the prediction of properties of the Substance and you concluded that the *"possible presence of a specific alcohol metabolite available at a level to exert a potential adverse effect on the liver is considerably diminished"* by the physiological alcohol detoxification pathways.

You also acknowledged in your read-across justification documentation the lack of bridging studies to support your read-across approach. You considered that "*all information needed to support the justification of the structural similarity has been generated by applying in silico methods and extracted from experimental studies available for the selected source compounds*".

Bridging studies provide relevant and reliable information allowing to compare the properties of the Substance and source substances and to assess the impact of exposure to all the

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

constituents of the Substance and source substance(s) and their metabolites on their toxicological properties.

As acknowledged in your comments to the draft decision and in the read-across justification documentation, no bridging studies are currently available to assess the impact of exposure to all the constituents of the Substance and of the source substance on their toxicological properties.

In your comments to the draft decision and in the read-across justification documentation you refer to *in silico* predictions on ADME properties to support similarity in toxicological properties between the Substance and the sourse substances.

Whilst information from *in silico* models may constitute relevant information in support of the read-across approach, considering the complexity of the endpoints under consideration these predictions cannot be seen, on their own, as evidence of similarity in the properties of these constituents.

Concerning the ADME predictions, a major metabolic pathway including three steps was specified in your technical dossier and in your comments. However, rates and extent of each step was not characterised. Non-common degradation products were identified as being formed through this pathway: alcohol and di/mono-esters. One of the alcohols formed from the constituents of the Substance gives rise to alerts for hepatotoxicity.

In your comments to the draft decision, you assume that the predicted concentrations of hepatotoxic metabolites are unlikely to cause potential adverse effects on the liver. However you have not provided information to support your assumption other than expected concentration levels of constituents associated with the formation of potentially hepatotoxic metabolites. Hence, in the absence of such information, the impact of the presence of potential hepatotoxic metabolites on the toxicity of the Substance cannot be reliably predicted.

As indicated above, the data set reported in the technical dossier does not include relevant, reliable and adequate information to compare the properties following repeated exposure for your Substance and the source substances, e.g. bridging studies of comparable design and duration.

In the absence information on the properties of the Subtance following repeated exposure, you have not established that the Substane and the source substances are likely to have similar properties for the endpoint under consideration.

Conclusion

For the reasons presented above and on the bases of the information provided in your registration dossier, ECHA considers that there is not sufficient support for your proposal that the Substance and the source substances have similar toxicological properties as result in structural similarity, common breakdown products, and similarity in physico-chemical properties. For these reasons, ECHA considers that your hypothesis is not a reliable basis whereby the properties of the the Substance may be predicted from data for reference substance. Therefore, your adaptation is rejected.

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 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 analogue approach and provided experimental studies according to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) with source substances tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate ("TM8-10") (EC 290-754-9) and Tris (2-ethylhexyl) 1,2,4-benzenetricarboxylate ("TOTM") (EC 220-020-0), and read-across documentation.

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

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 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-2114382253-51-01/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.

ECHA took into account your comments and did not amend the request(s).

Comments of procedural nature (referring to a cease of manufacture and transfer of the lead registrant role) which do not relate to the content of this decision, have been addressed in a separate communication to you.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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.