~~Confidential~~

Helsinki, 14 March 2022

Addressees
Registrant(s) of JS_431-700-8 as listed in the last Appendix of this decision

Date of submission for the submitted dossier subject to this decision
Date of submission subject to follow up evaluation, update by the new Lead Registrant: 29 May 2020

Registered substance subject to this decision ("the Substance")
Substance name: (1S,1'R)-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxycarbonyl]methyl propanoate
EC number: 431-700-8

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

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

By the decision of 26 April 2017 ("the original decision") ECHA requested you to submit information by 3 May 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 dossier 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 modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy**

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

Reasons for the request are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex IX of REACH".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They have the duty under Articles 125 and

126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[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 A: Reasons to request information required under Annex IX of REACH

You were requested to submit information derived with the registered substance for repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

On 5 August 2020 you submitted a dossier update and provided a sub-chronic toxicity study (90-day), oral route in rats with the registered substance.

However, the study you submitted did not include the immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy. In the endpoint study summary record, you indicate that "*Immunohistochemistry for alpha-2u globulin in the kidney was not successful in the main study animals, thus, despite the highly suggestive morphologic appearance of the male rat-specific 'hyaline droplet nephropathy' this cannot be confirmed. IHC of alpha 2 globulin was successful in the kidney of the recovery animals. Difference in duration of preservation in 10% neutral buffered formalin of the kidneys between main and recovery animals probably caused the difference in staining success. The use of two antigen retrieval steps before IHC staining did not improve the staining for the main study animals. Although positive staining for alpha-2u globulin via IHC was detected in the recovery animals, it was comparable to the concurrent control animals and thus was interpreted to be within background levels for male rats*."

You concluded that findings in the male kidneys were mediated by alpha-2u globulin and, therefore, not relevant to humans. Based on that assumption and, due to the lack of other relevant adverse effects, you established the NOAEL at the highest dose tested, 1100 ppm.

ECHA considers that, based on the provided information, it cannot be concluded that the findings in male kidneys are mediated by alpha-2u globulin nephropathy, and consequently, considered as non-relevant to humans. Further, as explained in the original decision, "*the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment".* Therefore, the results of the IHC for alpha-2u globulin are crucial for the NOAEL selection.

In your comments to the draft decision, you expressed the intention to repeat the immunohistochemistry for alpha-2u globulin in the kidney. More specifically, you state that the paraffin-embedded kidney samples will be transferred to another CRO with more experience on this test. The samples will then be processed and stained again.

ECHA agrees that a valid and reliable immunohistochemistry analysis of alpha-2u globulin nephropathy is needed to conclude on the involvement of alpha-2u-globulin in the kidney effects.

However, ECHA will only be able to conclude on the validity of your proposed approach and to assess the compliance of any information provided once you have been updating your registration dossier with the new information.

Based on the above, the request in the original decision was not met, and you are still required to provide information on a repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats with the registered substance modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

Notes for your consideration:

ECHA notes that the investigation to determine if the renal pathology is mediated by alpha-2u globulin nephropathy is an essential condition for the fulfilment of the request in this decision. Consequently, the information provided in response to the original decision cannot be considered as compliant at this point in time. Therefore, we invite you to address the specific deficiency outlined above, by generating the missing confirmatory information.

Alternatively, as indicated to you during an informal discussion on 10 November 2020, in the absence of the IHC of alpha 2 globulin, the findings observed in the kidneys should be considered as relevant to humans, and, consequently, the NOAEL should be established at the lowest dose. In that case, the Chemical Safety Report should also be modified accordingly.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[3].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals

Appendix C: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 26 April 2017 ("the original decision"). 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.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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).

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 D: List of references - ECHA Guidance[5] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[8]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.