EUROPEAN CHEMICALS AGENCY

Helsinki, 14 August 2020

Addressees
Registrants of TMPDM_25265-77-4_SIEF listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
23/01/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Isobutyric acid, monoester with 2,2,4-trimethylpentane-1,3-diol
EC number: 246-771-9
CAS number: 25265-77-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***19 November 2021***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490).

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annexe VIII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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.

Appendix A: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test. You have provided negative results for both Ames tests - OECD TG 471 ([redacted] 1995; [redacted] 1985) and, in the absence of an *in vitro* cytogenicity study, an *in vivo* cytogenicity study - OECD TG 474 ([redacted] 1992).

ECHA understands that you have provided an adaptation using a grouping and read-across approach.

You have provided a read-across justification in IUCLID Section 7.6 and CSR Section 5.7.3.

You read-across between the structurally similar substances, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB), EC No. 229-934-9 (CAS No. 6846-50-0) as source substance and the Substance as target substance.

The source study that you refer to in your read-across approach, an *in vitro* mammalian cell gene mutation assay, corresponds to a guideline study performed according to the OECD TG 476.

You have provided the following reasoning for the prediction of toxicological properties:
"[...] Based on the in vitro hydrolysis of isobutyric acid, monoester with 2,2,4-trimethylpentane-1,3-diol to TMPD and a similar in vivo metabolic profile for the diisobutyrate (TXIB™), available in vitro mammalian mutagenicity data for TXIB™ should also be considered in the overall genetic toxicity evaluation of isobutyric acid, monoester with 2,2,4-trimethylpentane-1,3-diol.[...]".

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case an OECD TG 476. These key parameters include:

- Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
- The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
- At least 4 concentrations must be evaluated, in each test condition.
- One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the

concurrent negative control.
- The response for the concurrent negative control must be inside the historical control range of the laboratory.
- Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

You have submitted a study based on a guideline corresponding to OECD TG 476 with basic information (e.g., "vehicle and positive controls induced the appropriate responses") but without detailed information on the coverage of any of the key parameters above.

You have not demonstrated that the provided study fulfills the key parameters of OECD TG 476. In the absence of this information, the results of this study are considered unreliable and thus rejected.

Missing supporting information

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[2] and related documents[3, 4].

ECHA notes the following shortcoming(s) with regards to prediction(s) of toxicological properties.

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[5]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include, in particular, toxicokinetic information on the formation of the common compound.

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[2] 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

[3] 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)

[4] 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

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

Missing information on the formation of common compound and on the impact of the non-common compounds

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, information characterising the rate and extent of the hydrolysis of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common hydrolysis product and to assess the impact of the exposure to the parent compounds.

To support your read-across hypothesis, you have provided the following information in your dossier:

i. An *in vitro* hydrolysis study in rat and human blood with the Substance (1989)

You state that "*In vitro, isobutyric acid, monoester with 2,2,4-trimethylpentane-1,3-diol [Texanol] undergoes partial hydrolysis in whole rat or human blood to produce the expected diol, TMPD.*" Furthermore, you indicate that "*Approximately 35.5% of the starting material did not undergo hydrolysis in either rat or human blood under conditions of this study*" and the study (i) concludes that "*The results of these in vitro studies suggest that the 1-substituted and 3-substituted isomers of Texanol may differ in their metabolic uptake, distribution, metabolism, and elimination.*"

You have not provided any information on the impact of the exposure to the parent compounds.

Also, regarding the *in vivo* study with TXIB, you conclude that "*Disposal of TXIB™ appears to involve some non-absorption and partial hydrolysis in the gut based on the occurrence of both TXIB-3-[14] C and a mono-isobutyrate ester of TMPD in the feces*".

Finally, the *in vitro* study with Texanol (i) shows a half-life of the 1-isomer of 19.6 and 17.3 minutes in rat and human blood, respectively, while the description of the *in vivo* study with TXIB in your read-across justification does not indicate any kinetic parameters. The percentage of recovery of TMPD, when administered separately, is 88% in the urine (and 2% in the feces) within 48 hours of dosing. There is no conclusive information on the rate of hydrolysis of both substances to allow for a comparison between the target and source substances.

ECHA notes, however, the following:

First, the information contained in (i) and your read-across justification shows that both Texanol and TXIB are not fully metabolised to 2,2,4-trimethyl-1,3-pentanediol (TMPD). Since you have not provided conclusive information on complete metabolic convergence of the target and source substances, your read-across hypothesis based on a toxicity exclusively due to the effect of the common TMPD metabolite cannot be confirmed.

Second, this information does not exclude that the parent substances Texanol and TXIB could contribute to the observed toxicity. Since un-reacted Texanol and TXIB could be responsible for the observed toxicity, different substance-specific effects, including genotoxic effects, cannot be excluded.

Third, regarding the kinetic parameters, the limited information available on hydrolysis rates of the esters does not allow a comparison between the Substance and the source substance.

In addition, differences in metabolisation of the di-ester to the two mono-esters may lead to a different ratio of mono-esters *in vitro/in vivo* as compared to testing of the Substance.

On this basis, you have not provided sufficient supporting evidence establishing that the proposed common hydrolysis product is formed to the extent assumed in your read-across hypothesis. Furthermore, you have not provided information characterising the exposure to the non-common compounds, including the parent compounds, resulting from partial hydrolysis of the Substance and of the source substance, and the impact of this exposure. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your read-across approach is rejected.

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

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[6].

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[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

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.

The compliance check was initiated on 17 June 2019.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments within the notification period.

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[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

OECD Guidance documents[10]
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.

[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.