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 a 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 TPE-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***23 May 2022.***

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

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

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408), in rats, and modified to include urinalysis and immuno-histochemical investigation of renal pathology allowing the determination of whether the pathology is mediated by alpha-2u globulin nephropathy;

B. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit), oral route;

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

- Appendices entitled "Reasons to request information required under Annexes IX to X of REACH", respectively.

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 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 IX of REACH

This decision is based on the examination of the testing proposals you submitted.

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.), in rats, with the Substance, and modified to include urinalysis and immuno-histochemical investigation of renal pathology allowing the determination of whether the pathology is mediated by alpha-2u globulin nephropathy**

A sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX, Section 8.6.2. to REACH.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the Substance.

ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement for which testing is proposed. ECHA has taken these considerations into account.

You proposed testing by the oral route, in rats. ECHA agrees with your proposal. According to OECD TG 408, the rat is the preferred species and the most appropriate route of administration is the oral route[2]. More specifically, although the information you provided in the dossier indicates that human exposure to the Substance by the inhalation route is likely, the available oral studies indicate a concern for systemic toxicity, in particular liver and kidney toxicity, that requires further information on repeated dose toxicity by the oral route.

Additionally, urinalysis and immuno-histochemical investigation of renal pathology is required to establish the relevance of the kidney effects for risk assessment[3].

In the studies you submitted, kidney weight and histopathological changes were observed in the kidneys of male rats and not in male control rats or in any exposed/control female rats:

- In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), increases in mean absolute and relative kidney weights were reported in the high-dose male rats and hyaline droplet formation, increased incidence of regenerative tubular epithelium, increased incidence of dilated tubules and the presence of granular casts at the cortico-medullary junction were observed in the mid- and high-dose male rats.
- In the 28-day repeated dose toxicity study (OECD TG 407), cortical tubular eosinophilic inclusions were observed in in the kidneys of the two higher-dose male groups.
- In the sub-acute toxicity study, hyaline droplet degeneration was observed in the kidneys of all treated male rats.

This indicates that the kidney is a target organ of the Substance which may induce alpha-2u-globulin-mediated nephropathy. Since this mode of action is considered not relevant to humans, 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.

[2] ECHA Guidance R. 7a, Section R.7.5.4.3.
[3] ECHA Guidance R. 7a, Section R.7.5.6.3.4

Therefore, ECHA considers that a urinalysis (described in paragraph 37 of OECD TG 408) is required to investigate further the kidney function after administration of the Substance. Additionally, a full histopathological examination (paragraphs 45 and 47 of OECD TG 408), including immune-histochemical investigation of renal pathology is required to determine if the pathology is mediated by alpha-2u globulin.

In your comments you agree to perform this test. ECHA acknowledges your agreement.

You further explain that 12 months is not an adequate time to perform this request, due to the immunohistochemical staining for a2u. Unlike "normal" staining with a chromogen-based stain, antibody-based staining has 2 major hurdles. First, the supply of the primary antibody must be available, and that is never a given. If the primary is not available, the staining is delayed. Second, every time such staining is undertaken, the staining process must be optimized to maximize the signal to noise ratio, and also, in many cases, such techniques as antigen retrieval may be needed to maximize the signal.

ECHA agrees with your request and has extended the deadline.

According to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the proposed test under modified conditions, as explained above. The test must be carried out with the Substance and with inclusion of urinalysis and immune-histochemical investigation of renal pathology allowing the determination of whether the pathology is mediated by alpha-2u globulin nephropathy.

Appendix B: Reasons to request information required under Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2., column 2) in a second species

Pre-natal developmental toxicity (PNDT) studies on two species is a standard information requirement under Annex X, Section 8.7.2 to REACH.

You have submitted a testing proposal for a PNDT study in a second species (rabbits) according to OECD TG 414 by the oral route with the Substance.

You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study fulfils the information requirement.

You proposed a study with the rabbit as a second species. The rat or rabbit is the preferred species under the OECD TG 414. The study in the first species was carried out with rats. On the basis of this default consideration, the study should be performed with the rabbit as a second species.

You proposed administration by the oral route. ECHA agrees with your proposal.

The oral route is the most appropriate route of administration to investigate reproductive toxicity[4].

In your comments you agree to perform the test. ECHA acknowledges your acceptance.

Under Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test with the Substance.

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.

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Appendix C: 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[5].

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[6].

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

Appendix D: Procedure

Your submitted testing proposal for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 4 April 2019

ECHA held a third party consultation for the testing proposals from 26 April 2019 until 10 June 2019. ECHA did not receive information from third parties.

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.

In your comments you explained that 12 months is not an adequate time to perform the request for an OECD TG 408 study according to the specifications made by ECHA. This is due to the immunohistochemical staining for a2u. Unlike "normal" staining with a chromogen-based stain, antibody-based staining has 2 major hurdles. First, the supply of the primary antibody must be available, and that is never a given. If the primary is not available, the staining is delayed. Second, every time such staining is undertaken, the staining process must be optimized to maximize the signal to noise ratio, and also, in many cases, such techniques as antigen retrieval may be needed to maximize the signal.

ECHA took into account your comments and amended the deadline of A1 request, 90-day toxicity study from 12 months to 18 months. The draft decision deadline for both A1 and B2 requests is 18 months.

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 E: List of references - ECHA Guidance[7] 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)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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.

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

OECD Guidance documents[9]

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.

[9] 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]

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.