ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 31 July 2020

Addressees
Registrants of JS 16883-83-3 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
06/09/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction Mass of Benzyl (1R,1S) 2,2,4-trimethyl-1-[(2-methylpropanoyl)oxy]pentan-3-yl benzene-1,2-dicarboxylate and Benzyl (3R,3S) 2,2,4-trimethyl-3-[(2-methylpropanoyl)oxy]pentyl benzene-1,2-dicarboxylate
EC number: 701-008-3
CAS number: NS

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 ***8 August 2022***.

A. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral (gavage) route, specified as follows:

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which must be followed to weaning and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You must report the study performed according to the above specifications. Any expansions of the study design must be scientifically justified.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

- Therefore you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information they are required to submit to fulfil the information requirements for their registration.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

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

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, has to 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.

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 for the requirement applicable to all the Registrants subject to Annex X of REACH

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

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)**

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats with 10-week premating exposure duration. You have provided the following justification and specification of the study design according to the criteria described in Column 2 of Section 8.7.3, Annex X, and detailed in ECHA Guidance R.7a: *"It is proposed that the study will be carried out in rats using oral (gavage) administration and will follow the basic study design outlined in EU method B.56/OECD 443. Dose levels will be selected based on evaluation of existing sub-chronic and other repeat dose toxicity data available for the substance being tested and/or closely related materials, subject to a maximum dose of 1000 mg/kg/day. The pre-mating exposure period will be at least 10 weeks, in accordance with existing ECHA guidance (ECHA, 2017)."* Furthermore, you consider that as there is potential for significant exposure of professional users or consumers under normal conditions of use, and extended exposure is needed to reach steady state kinetics, *"Consequently, extension of the basic study design to evaluate the F2 generation will be required."*. You also consider that evaluation of developmental neurotoxicity or immunotoxicity is not required.

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

The proposed study design requires modification to fulfil the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed *"The pre-mating exposure period will be at least 10 weeks, in accordance with existing ECHA guidance (ECHA, 2017)."* ECHA agrees with your proposal. Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance R.7a. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance to ensure that the steady state in parental animals has been reached before mating.

You propose that *"Dose levels will be selected based on evaluation of existing sub-chronic and other repeat dose toxicity data available for the substance being tested and/or closely related materials, subject to a maximum dose of 1000 mg/kg/day."*

It is your responsibility to select dose levels that meet the criteria described below.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals,

to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

Extension of Cohort 1B

If the Column 2 conditions of Section 8.7.3., Annex X are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

You proposed to include an extension of Cohort 1B and provided justification following Column 2 criteria.

ECHA agrees that the criteria to extend the Cohort 1B are met, because:

- The use of the Substance leads to significant exposure of consumers and professionals because the Substance is used by professionals in roller applications, brushing, treatment of articles by dipping and pouring (PROCs 1, 2, 3, 4, 5, 8b, 9, 10, 13) and consumers as coatings and paints, thinners, paint removers, adhesives and sealants.

- In addition, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. The calculated log Kow of the Substance is 7.0, and the technical dossier concludes that the Substance is "*potentially Bioaccumulative (B) and/or very Bioaccumulative (vB)*".

- Finally, there are indications for endocrine-disrupting modes of action because of the thyroid findings in the OECD TG 408 study[2, 3], such as

    - increase in absolute and relative thyroid weight in both males and females (dose-related and statistically significant in males);
    - histopathologic changes in thyroid gland: follicular cell hypertrophy in mid and high dose males and females;
    - changes in relevant hormone levels: decreased T4 levels in mid and high dose males (statistically significant at high dose) and high dose females as well as dose related increase in TSH levels in males.
    - Also, there were changes in the HDL/LDL ratio in all treated groups of males.

Therefore, the Cohort 1B must be extended.

[2] Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150
[3] ECHA Guidance R.7a, Section R.7.6.

The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[4]. It is recommended to aim to 20 litter per dose group.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed not to include Cohorts 2A and 2B and provided justification following the Column 2 criteria.

However, ECHA considers that the criteria to include Cohorts 2A and 2B are met, because existing information on the Substance derived from available *in vivo* study (OECD TG 408) shows evidence of thyroid toxicity in both males and females. In particular, the study showed an increase in absolute and relative thyroid weight in both males and females (dose-related and statistically significant in males); there were histopathologic changes in thyroid gland: follicular cell hypertrophy in mid and high dose males and females; and there were relevant changes in thyroid hormone levels: circulating T4 level was reduced by 25.8% and 12% in high dose males and females, respectively. Concomitantly, there was a dose-dependent increase of TSH in treated males, reaching +102% at the high dose. TSH was also increased by 87% in high dose females. Furthermore, there were changes in the HDL/LDL ratio in all treated groups of males.

In your comments to the draft decision you argued that conditions to include developmental neurotoxicity cohorts (DNT, 2A and 2B) are not met. Regarding the OECD TG 408 study, you claimed: *"A 90d oral repeated dose toxicity (OECD 408 TG; [redacted] 2019)) with Santicizer®278 did not reveal any evidence of adverse effects on the nervous system or any concern for developmental neurotoxicity."* Furthermore, you stated that the effects observed in the liver and the thyroid gland are commonly observed as an adaptive response associated with the metabolism of xenobiotics or their metabolites ([redacted] 2012; [redacted] 2012) and therefore claimed that the thyroid effects seen in the OECD TG 408 study are due to enzyme induction in the liver.

ECHA considers that signs of thyroid toxicity or relevant changes in thyroid hormone levels may indicate a particular concern on developmental neurotoxicity and justify the inclusion of Cohorts 2A and 2B (ECHA Guidance R.7a[5]). The available information shows clear changes in thyroid organ weight, histopathology and hormone levels of treated animals, which supports triggering. The possibility that thyroid toxicity may be secondary to the liver does not remove the concern.

The developmental neurotoxicity cohorts 2A and 2B must be conducted because there is a particular concern on (developmental) neurotoxicity.

Species and route selection

You proposed testing by oral (gavage) route in rats. ECHA agrees with your proposal.

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4 http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

5 ECHA Guidance R.7a, Appendix R.7.6-2 EOGRTS Study Design.

Outcome

Under Article 40(3)(b) of REACH, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance.

In your comments, you have provided information on physico-chemical and toxicological properties of structural analogues to the Substance and you state that there will be an update of the registration dossier in January 2020, including a read-across justification. Deviating from your original testing proposal, you have requested to perform the OECD TG 443 study with the structurally analogous read-across substance (Santicizer® Platinum P1700).

You have not provided any read-across justification that would support your reasoning for comparable physico-chemical and toxicological properties between the Substance and Santicizer® Platinum P1700. Thus, the provided information does not allow ECHA to assess and conclude that testing on that substance would predict the relevant toxicological properties of your registered Substance. In the absence of such critical elements of read-across, you are requested to carry out the proposed test with the Substance.

Further expansion of the study design

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3 if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

[6] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 28 February 2019.

ECHA held a third party consultation for the testing proposal from 27 May 2019 until 11 July 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 within 30 days of the notification.

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

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 C: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State(s).

3. Test guidelines, GLP requirements and reporting

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

   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.

   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: 'How to report robust study summaries'[7].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have 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.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

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.

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

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

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

Appendix D: 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 fulfilled
[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.