EUROPEAN CHEMICALS AGENCY

Helsinki, 21 August 2020

Addressees
Registrants of JS_TMBPF-DGE listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
13 November 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction mass of 2,2'-{methylenebis[(2,6-dimethyl-4,1-phenylene)oxymethylene]}dioxirane and 1,3-bis{4-[3,5-dimethyl-4-(oxiran-2-ylmethoxy)benzyl]-2,6-dimethylphenoxy}propan-2-ol and 3,3'-{methylenebis[(2,6-dimethyl-4,1-phenylene)oxy]}bis(1-{4-[3,5-dimethyl-4-(oxiran-2-ylmethoxy)benzyl]-2,6-dimethylphenoxy}propan-2-ol)
EC number: 941-357-0
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 ***28 November 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 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) without extension to mate the Cohort 1B animals to produce the F2 generation; 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

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- 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.

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 proposals 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. 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:

- Premating exposure duration for parental (P0) animals: 10 weeks.
- Basis for dose level selection: the results of the OECD TG 408 and 422 studies. *"If deemed necessary an additional dose range finder may be performed if additional data are needed for dose level selection."*
- Inclusion/exclusion of extension of Cohort 1B: you state that the criteria for extension are not met.
- Termination time for F2: This is not applicable as the extension of cohort 1B to include the F2 generation is not proposed.
- Inclusion/exclusion of extension of Cohort 2A and 2B: you state that the criteria for inclusion are not met.
- Inclusion/exclusion of extension of Cohort 3: you state that the criteria for inclusion are not met.
- Route of administration: oral.
- Species and strain: rat Wistar. *"The strain selection for the available OECD 422, 414 and 408 studies were Wistar (Crl:WI(Han) strain rats) and it is preferred that this strain is used for the EOGRTS."*

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 10 weeks premating exposure duration.

ECHA considers that ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance R.7a.

You propose to choose the dose levels based on the OECD TG 408 and OECD TG 422 studies and state that *"The high dose selected [...] would likely show evidence of systemic toxicity but not cause excessive mortality"*. ECHA notes that it is your responsibility to select the dose levels that meet the criteria described below in order to obtain informative results for hazard

classification and labelling (CLP Regulation 1272/2008) as well as for risk assessment purposes.

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.

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 must be included.

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 the cohorts 2A and 2B providing the following justification: *"Results from the available OECD 422, 408 and 414 studies did not indicate adverse primary effects on the nervous system. This included no adverse changes in applicable clinical observations, brain weights, neuropathology (brain, spinal cord, nerves etc.) nor any adverse developmental effects. There was also no adverse effect on the functional observation battery (FOB) nor motor activity or locomotor endpoints observed on the appropriate studies. Any relevant findings noted were considered non-adverse in nature and/or linked to adaptive responses."*

However, ECHA considers that the criteria to include Cohorts 2A and 2B are met, because existing information on the Substance derived from available OECD TG 408 study shows evidence of thyroid toxicity: increase in thyroid weight accompanied by histopathological changes, i.e. hypertrophy within the follicular epithelial cells in male and female rats. Signs of thyroid toxicity rise a particular concern on developmental neurotoxicity (ECHA Guidance R.7a). In addition, you reported dose-dependent decrease in the forelimb grip strength in male rats (statistically significant at mid and high dose).

In your comments to the draft decision you *"reject the assessment by ECHA that the DNT cohort is required"*. In support of your rejection you state that:

(i) The thyroid effect is *"considered an adaptive response secondary to effects observed in the liver"*. Further, you provide the statement of the GLP study report author of the OECD TG 408 study that "[...] *findings within the liver and thyroid were consistent with hepatic enzyme induction/adaptation (Hall et al., 2012; Maronpot et al., 2010)."* You conclude that *"enzyme induction in the liver and subsequent secondary effects are of little relevance to man."*

(ii) Decrease in the forelimb grip strength in the 90-day study was *"[...] observed in association with decreased food consumption and bodyweight gain both of which can affect these endpoints (Maurissen et al., 2003; Ross, 2000; IPCS 2001)"* and *"was only observed in males and with no associative gross or histo/neuropathological correlate"*. You further claim that no adverse effects on the forelimb grip strength were observed in the available OECD TG 422 study.

You conclude that based on a weight-of-evidence analysis and on peer reviewed publications, your Substance "*is not deemed to possess neurotoxic potential and accordingly is unlikely to cause developmental neurotoxic effects*" and you request ECHA to remove the DNT cohort request from the draft decision.

Firstly, regarding your statement that the changes in the thyroid gland (organ weight and histopathology) are adaptive and secondary to the liver changes, ECHA has the following observations:

In the OECD TG 408 study, males seemed to be more sensitive to the thyroid effects than females: males showed effects in the thyroid already at 300 mg/kg bw/day whereas in females effects were observed only at 600 mg/kg bw/day.

Based on the reported data, there is no established relationship between the changes in the liver and the thyroid gland in both male and female rats. On the contrary, for example in the 300 mg/kg bw males the thyroid weight was increased by 38%, with follicular cell hypertrophy observed in 4/10 animals. These effects were not accompanied by any changes in the liver: at this dose, the liver weight was decreased by 1%, and hepatocyte hypertrophy was observed in 0/10 animals. The following changes were observed in liver enzyme activity: aspartate aminotransferase +8%, alanine aminotransferase +28%, gamma glutamyl transferase showed no change, and alkaline phosphatase -7%. In 300 mg/kg bw/day females, the statistically significant increase (+26%) in the liver weight and 10/10 animals showing hepatocellular hypertrophy were not accompanied by changes in the thyroid gland. Therefore, your claim that the effects on the thyroid gland are secondary to the liver effects, is not supported by the available data.
On the potential relevance of the findings to man, ECHA considers that "*Substances inducing histopathological changes (i.e. follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring.*" and "*In the absence of substance-specific data which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption (including cases where liver enzyme induction is responsible for increased TH clearance).*"[2]

Further, you claim that the decrease in the forelimb grip strength in males in the 90-day study is related to a decreased food consumption and body weight gain.

You have reported a dose-dependent decrease in forelimb grip strength in males (-16.3% in low dose, -26% in mid dose and -34.6% in high dose; the changes were statistically significant at the mid and high dosed animals). You have reported in your dossier that "*At the end of the dosing phase, overall bodyweight gain was lower in males administered 100, 300, or 600 mg/kg/day (12%, 7%, and 24%, respectively)*". Your dossier further states that "*Lower body weight gain was limited to first few weeks of the dosing phase for males administered 300 mg/kg/day and was subsequently comparable with controls.*" ECHA further notes that compared to the control animals, the terminal body weights were 7.6%, 4.9% and 14.6% lower in low, mid and high dose males, respectively. In addition, the decrease in the mean food consumption is defined as "*minimally lower*" (9 or 4% at mid and high dose, respectively) which cannot be regarded as "*diet restriction*" (Maurissen et al., 2003).

[2] Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA) with support from the Joint Research Centre (JRC). EFSA Journal 2018;16(6):5311

The reported data does not support your claim that the observed decrease in the forelimb grip strength is only related to the changes in the food consumption and body weight gain.

You further state that similar effects were not reported in the OECD TG 422 study.

In the OECD TG 422 study, the males were exposed for 29 days, whereas in the OECD TG 408 study the exposure duration was 91 days. Therefore, as the exposure duration is significantly longer in the OECD TG 408 study, the results of the OECD TG 422 study are not directly comparable.

Therefore, 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 route in Wistar rats, in line with the available OECD TG 422, 414 and 408 studies. ECHA agrees with your proposal. The findings from the OECD TG 408 study must be followed in an EOGRT study with the same rat strain and the same route of administration.

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.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or 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 IX/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[3].

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

Appendix B: Procedural history

ECHA received your registration containing the testing proposal for examination on 2 September 2019.

ECHA held a third party consultation for the testing proposal from 21 October 2019 until 5 December 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(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 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'[4].

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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[5].

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

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)[7]

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.

[5] https://echa.europa.eu/manuals
[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] 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.