EUROPEAN CHEMICALS AGENCY

Helsinki, 10 February 2020

Addressees
Registrants of CAS_119345-04-9_JOINT listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
15 November 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Benzene, 1,1'-oxybis-, tetrapropylene derivs., sulfonated, sodium salts
EC number: 601-601-6
CAS number: 119345-04-9

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 ***18 May 2023***.

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

You are requested to perform additional study:

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

B. Requirements applicable to 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 or rat), oral route;

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance 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); and
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

   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 IX of REACH, if you have registered a substance at 100-1000 tpa;
- 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 requirements applicable to all the Registrants subject to Annex IX of REACH

This decision is based on your proposals for testing for Reproductive toxicity and the examination of the technical dossier content.

ECHA understands that in the dossier you have provided a Pre-natal developmental toxicity study performed with rats, and that you therefore considered the proposed testing on rabbits as testing on a second species. In the following ECHA states the reasons for why also a study in a first species is requested, before considering the proposed testing on a second species as well as the proposal for an extended one-generation reproductive toxicity study in Appendix B.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pre-natal developmental toxicity (PNDT) study in one species is a standard information requirement in Annex IX to REACH.

You have provided Chernoff-Kavlok teratogenicity screening test ([redacted] 1985) conducted in rats with an analogue substance Benzene, 1,1'-oxybis-, sec-hexyl derivs., sulfonated, sodium salts, EC No. 429-650-7 (C6 linear ADPODS, sodium salt; CAS No. 147732-60-3).

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

In your registration dossier you have formed a group (category) of 'Alkyl Diphenyl Oxide Disulfonates (ADPODS)'. You have provided a read-across justification document in IUCLID Section 13.

In your comments on the draft decision you have not provided any new information related to your read-across justification. You have re-submitted exactly the same read-across justification document, which ECHA has already assessed and in relation to which the deficiencies has been noted below.

Your category approach covers the following substances:

[i] Benzene, 1,1'-oxybis-, sec-hexyl derivs., sulfonated, sodium salts, EC No. 429-650-7 (C6 linear ADPODS, sodium salt; CAS No. 147732-60-3; i.e. the source substance);

[ii] Benzenesulfonic acid, decyl(sulfophenoxy)-, sodium salt (1:2), EC No. 253-040-8 (C10 linear ADPODS, sodium salt; CAS No. 36445-71-3)

[iii] Benzene, 1,1'-oxybis-, tetrapropylene derivs., sulfonated, sodium salts, EC No. 601-601-6 (C12 branched ADPODS, sodium salt; CAS No. 119345-04-9; i.e. the Substance)

[iv] Benzenesulfonic acid, (oxybis)hexadecyl(sulfophenoxy)-, sodium salt (1:2), EC No. 405-430-6 (C16 linear ADPODS, sodium salt; CAS 65143-89-7 (mono-, major) and 70191-76-3 (di-,minor))

You have provided the following reasoning for the prediction of developmental toxicity properties in your read-across justification, under 'Rationale for Category Grouping': *"The toxicological dataset from the shortest C6 alkyl Category member constitutes the most conservative case for mammalian read-across [...] The read-across for the developmental endpoint for the ADPODS Category members is thus based on the data from the shortest C6".*

In addition, under the 'Characterization of the ADPODS Category' you mention a hypothesis based on the (bio)transformation and you state that *"Category Approach based on the (bio)transformation to common compounds hypothesis for read-across is applied for the ADPODS Category members."* However, you have not identified what are the common product(s) that would drive the impact on the property under consideration or considered the impact of compositional and structural differences between the substances on the (bio)transformation, nor have you provided any experimental evidence to support such an alternative hypothesis.

Therefore, we understand that you intended to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on a worst-case approach.

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. Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

We have assessed your adaptation and note the following deficiencies with regards to the prediction of toxicological properties.

Missing supporting information

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"*[2]. 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 other category members.

Supporting information must include information to confirm your claimed worst-case prediction. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance.

To support your read-across hypothesis you have provided screening studies for reproductive/developmental toxicity using the source substance (C6 linear ADPODS, sodium salt) and the category member C16 linear ADPODS, sodium salt. However, the data provided in these studies do not confirm the proposed worst-case prediction. In addition, you have not provided any explanation on why the substance with the shortest alkyl chain length, i.e. the source substance, is expected to lead to conservative predictions of the properties of the Substance.

Furthermore, the data set reported in the technical dossier does not include any information on the Substance that support your read-across hypothesis for the properties under consideration. No assessment or considerations on the impact of the structural differences between the source substance and the Substance have been reported.

[2] ECHA Guidance R.6, Section R.6.2.2.1.f.

In the absence of this information, you have not established that the source substance constitutes a worst-case for the prediction of the properties under consideration of the Substance. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Adequacy and reliability of the 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:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the source study has to meet, among others, the following key parameters of OECD TG 414:

- examination of external, skeletal and soft tissue alterations (variations and malformations); and
- testing of at least three dose levels and a concurrent control.

Your source study is a non-guideline (GLP compliant) developmental Chernoff test conducted in rats (Key study, [redacted], 1985) using the source substance (purity 41.9%; oral gavage) at the doses of 1000 or 300 mg/kg/day (gavage from GD 6 through GD 15). A developmental NOEL of >1000 mg/kg/day was reported based on no developmental adverse effects at the highest dose tested. However, the above key parameters as required by OECD TG 414 are not met:

- the external, skeletal and soft tissue alterations (variations and malformations) have not been examined; and
- the testing considered only two dose levels and a control.

ECHA concludes that the conditions set out for the results to be read-across in the Annex XI, Section 1.5. are not met; therefore no reliable predictions can be made using this study.

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

Therefore, the information requirement is not fulfilled.

Outcome

Under Article 40(3)(c) of the REACH Regulation, you are requested to carry out an additional PNDT study according to the test method OECD TG 414 performed in rat or rabbit as preferred species with oral[3] administration of the Substance.

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

Appendix B: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of your proposals for testing for Reproductive toxicity and the examination of the technical dossier content.

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

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) on two species is a standard information requirement under Annex X to REACH.

You have submitted a testing proposal for a PNDT study in a second species according to OECD TG 414.

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 in the rabbit as a second species. The rat or rabbit is the preferred species under the OECD TG 414[3]. Testing should be performed with the rabbit or rat as a second species, depending on the species tested in the first PNDT study.

You proposed administration by the oral route. ECHA agrees with your proposal. The oral[3] route is the most appropriate route of administration to investigate reproductive toxicity.

Outcome

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

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2, column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species (the request for the 1st PNDT study notified to you under request A.1 of this decision) or any other new information enable such adaptation, testing in a second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. 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 EOGRT study according to OECD TG 443 by the oral route with the following justification and specification of the study design:

- *"OECD 443 study guideline is proposed to be followed";*
- *"the registered substance is proposed to be administered via the oral route to*

complement the existing dataset and as it is the expected most bioavailable route of exposure for the registered substance";
- *Since no triggers were identified that would warrant investigation of neurodevelopmental or immunodevelopmental toxicity, DNT and DIT cohorts are not proposed to be included in the experimental design of OECD 443 study"; and*
- *"Based on the WoE data for the ADPODS category members and the registered substance, extension of Cohort 1B to F2 is excluded from the proposed EOGRTS design"; and*
- *"Standard rat strain is being proposed for the EOGRTS design."*

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.

The proposed study design fulfils the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed standard exposure duration and dose levels selection based on the screening study data.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[4]

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall 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. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

ECHA notes that while you propose to select the dose levels based on the screening study data, you have not provided any such data with the registered substance. Therefore, if there is no 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 results that demonstrates 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.

Species and route selection

You proposed testing in rats via oral route. ECHA agrees with your proposal.

Outcome

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

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

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the 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[4].

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision you requested ECHA to extend the deadline by 6-12 months due to the laboratory capacity issues. From the documentary evidence from the laboratory, you further provided on ECHA request, it appears that the timeline of 30 months is sufficient to cover the sequential testing.

However, you have additionally explained that extension of the deadline is needed due to the test material issues. In particular, the Substance "is an aqueous mixture that will require drying down to a powdered form free of water, and only then can be used in analytical as well as subsequent test work. This activity in itself will require significant time and resource commitment".

ECHA has agreed with your request for the deadline extension due to availability of the test material and granted 6 months extension to the original deadline. Therefore, the deadline is set to 36 months.

Appendix C: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 16 July 2018, following the necessary clarification of the identity of your substance.

ECHA held a third party consultation for the testing proposals 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(s), but amended the deadline.

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: 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'[5].

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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[6].

5. List of references of the ECHA Guidance and other guidance/ reference documents[7]

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)[8]

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 GD23.

[6] https://echa.europa.eu/manuals
[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

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 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.