EUROPEAN CHEMICALS AGENCY

Helsinki, 19 August 2020

Addressees
Registrants of JS_C810trimellitate listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
16 May 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,2,4-BENZENETRICARBOXYLIC ACID, MIXED DECYL AND OCTYL TRIESTERS
EC number: 290-754-9
CAS number: 90218-76-1

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***29 May 2023***.

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance;

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Justification for an adaptation of a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1., column 2) based on the study requested under Section D.2.; with the Substance;

2. Long-term toxicity testing on fish also requested at C.2. below (triggered by Annex VIII, Section 9.1.3., column 2;)

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

1. Robust study summary of the Pre-natal developmental toxicity study in rats conducted with the Substance;

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance;

D. 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 (rat or rabbit), oral route with the Substance;

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the 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) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning.

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 Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and 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.

When a study is required under several Annexes of REACH, the reasons are provided in the corresponding appendices of this decision. The registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants in accordance with Article 53 of REACH.

Registrants are only required to share the costs of information that they must 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. The timeline has been set to allow for sequential testing where relevant.

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.

Authorised[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 on general considerations

Grouping of substances and read-across

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[2]

In your comments on the draft decision, you indicate that you intend to create a category approach with all (or at least the majority of) REACH registered Trimellitates to have a greater pool of data. The update will include new information on the composition of the substances and additional data on toxicokinetics, mammalian toxicity, biodegradability, bioaccumulation and environmental toxicity on the category members which have been generated in the context of other regulatory obligations.

ECHA acknowledges your intention to strengthen the read-across approach. However, without further details on the composition of the substances intended to be included in the category, detailed robust study summaries of all source studies used for the prediction, and the revised read-across justification, ECHA is unable to assess whether or not the new approach would comply with the Annex XI, Section 1.5. requirements.

Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. Therefore, 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.

[2] ECHA Guidance R.6: Section R.6.2.6.2

Appendix A: Reasons for the requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided a key study in your dossier:

i. [redacted], 1987 – Bacterial reverse mutation assay (similar to OECD TG 471) conducted with tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate, EC No. 268-007-3[3] (CAS No. 67989-23-5[3]; DOTM) using the following strains, *S. typhimurium* TA 97, TA 98, and TA 100, which all gave negative results.

We have assessed this information and identified the following issue:

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). The key parameter(s) of this test guideline include that the test must be performed with five strains: four strains of S. typhimurium (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

The provided data did not include results of the required 5 strains. TA1535 or TA1537 and TA102, E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) are missing.

The information provided does not cover the key parameters required by OECD TG 471.

In your comments on the draft decision, you indicate that you intend adapt this infromation requirement using a read-across adaptation. As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

[3] The previous identifiers for the Substance.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. Justification for an adaptation of the Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1., column 2)

Screening for reproductive/developmental toxicity is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

The present decision requests the registrants concerned to generate and submit an Extended one-generation reproductive toxicity study (EOGRTS) (see Appendix D, Section 2). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

In your comments, you agree to revise the justification for the adaptation based on the OECD TG 414, 408 and 443 studies.

2. Long term toxicity testing on fish also requested at C.2. below (triggered by Annex VIII, Section 9.1.3., column 2)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH. However, pursuant to Annex VIII, section 9.1.3, column 2, for poorly water soluble substances (e.g. water solubility below 1 mg/L) long-term toxicity study on fish (Annex IX, Section 9.1.6) must be considered instead of an acute test.

Poorly water soluble substances require longer time to reach steady-state conditions and the short-term tests may not give a true measure of toxicity for this type of substances.

You have estimated the water solubility of the substance to 0.6 ng/L. The results show that the Substance is poorly water soluble, i.e. has a water solubility below 1 mg/L.

Therefore, long-term toxicity testing is needed to accurately define the hazard of the Substance.

The examination of the adaptation, as well as the selection of the requested test and the test design are addressed in Appendix C, Section 2.

Your comment on the draft decision submitted for the request of long-term toxicity testing on fish is addressed in Appendix C, Section 2.

Appendix C: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

3. Robust study summary of the Pre-natal developmental toxicity study in rats conducted with the Substance

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided a Pre-natal developmental toxicity study in rat ([redacted] 2010) conducted with the Substance (identified with former CAS No). In the robust study summary, you have not provided detailed information of the results. You conclude that *"the test item caused a marked maternal toxicity as indicated by the reduction in food consumption, body weight, body weight gain, gravid uterus weight and absolute weight gain. As a consequence of the marked maternal toxicity, at the same* dosage*, foetal toxicity was present as demonstrated by the reduction in litter weight, foetal weight and delay in the ossification of different parts of the foetal skeleton. Visceral malformations detected in mid- and high dose groups were considered common findings in foetuses, that usually disappear shortly after birth and since the incidence was low and not dose-related, they did not show clear relationship to treatment and therefore were considered incidental."*

A robust study summary must be provided for the sole study available or, if more than one is available, for the study/ies giving rise to the highest concern (Articles 3(28) and 10(a)(vii) and Annex I, Section 1.1.4 of REACH).

A robust study summary must cover sufficient information to make an independent assessment of the study. Such an assessment requires tables which summarise all the results required by the OECD TG 414 with regard to:

i. Maternal toxic response data by dose;
ii. Developmental endpoints by dose for litters with implants; and
iii. Developmental endpoints by dose for litters with live fetuses.

Without this information the provided information cannot be accepted.

In your comments on the draft decision, you agree to improve the robust study summary.

On this basis, you must provide a robust study summary which contains the above missing elements for the study.

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Long-term toxicity testing on fish is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted this information requirement with the following arguments:

1) limited bioavailability of the substance
2) lack of chronic toxicity to Daphnia magna and algae,
3) QSAR predictions of no chronic toxicity to fish and
4) lack of chronic fish toxicity observed with worst case read across substances

(phthalates).

You state that this information used as a weight of evidence approach allows conclusion that the Substance will not cause chronic toxicity to aquatic life. ECHA understands that you have meant to adapt this information requirement by using weight of evidence according to Annex XI, Section 1.2.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow concluding on no toxicity to early life stages of fish for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an OECD TG 210 (stage of embryonic development, hatching and survival, appearance, behaviour, weight, length).

You have not provided any sources of information. The justification you have given in the form of arguments do not provide any data on the key parameters foreseen to be investigated in an OECD TG 210, as listed above.

In conclusion, none of your arguments alone or together allows to conclude whether the Substance has or has not hazardous properties related to lethal and sub-lethal effects to early-life stages of fish (stage of embryonic development, hatching and survival, appearance, behaviour, weight, length).

In your comments on the draft decision, you indicate that you intend adapt this infromation requirement using a read-across adaptation. As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is considered suitable.

In addition, please note that OECD GD 210 indicates that for difficult to test substances, the OECD Guidance Document No. 23 should be consulted.

Appendix D: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

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) in two species is a standard information requirement under Annex X to REACH.

You have provided a Pre-natal developmental toxicity (according to OECD TG 414) conducted in rats with the Substance.

For the information on a PNDT in a second species, you have adapted the information requirement using what ECHA understands to be weight of evidence approach (Annex XI, Section 1.2). In your justification the following independent sources of information and arguments are presented:

- results from Pre-natal developmental toxicity study in rats (OECD TG 414);
- results from Repeated dose toxicity studies in rats (OECD TG 407 and 408);
- A general argument that the rat is one of the rodent species that has proven to be extremely useful in pharmacologic and toxicologic research (based on Kacew and Festing, 19964); and
- An argument that due to animal welfare concerns testing is not necessary (based on Oberg et al., 20105).

Based on the presented lines of evidence you argue that testing is not necessary.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow concluding on pre-natal developmental toxicity in a second species for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an OECD TG 414 study in two species.

ECHA has assessed to what extent the information submitted enables a conclusion of hazardous properties for reproduction and identified the following deficiency:

None of the sources of information provides information on pre-natal developmental toxicity in other species than the rat.

In conclusion, none of the pieces of information alone or together allows to conclude whether the Substance does or does not have hazardous properties related to prenatal developmental toxicity in a species other than the rat.

In your comments on the draft decision, you indicate that you intend to create a category approach with all (or at least the majority of) REACH registered Trimellitates to have a greater

[4] Kacew S, and Festing MFW. Role of Rat Strain in the Differential Sensitivity to Pharmaceutical Agents and Naturally Occurring Substances. J. Toxicol. Environ. Health, 1996; 47:1–30.
[5] Oberg M, Benchmark dose approaches in chemical health risk assessment in relation to number and distress of laboratory animals. Reg Toxicol Pharmacol. 2010; 58: 451-4.

pool of data. The update will include new information on the composition of the substances and additional data on toxicokinetics, mammalian toxicity, biodegradability, bioaccumulation and environmental toxicity on the category members which have been generated in the context of other regulatory obligations.

ECHA acknowledge your intention to develop a the read-across approach. However, without further details on the composition of the Substances intended to be included in the category, detailed results of the additional studies, and the improved read-across justification, ECHA is unable to assess whether the approach would comply with the Annex XI, Section 1.5. requiremnts of REACH.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Information on study design

The test in the first species was carried out by using a rodent species (rat). A PNDT study according to the test method OECD TG 414 must be performed in rabbit as preferred non-rodent species.

The study must be performed with oral[6] administration of the Substance.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRTS; 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 adapted the information requirement using what ECHA understands to be weight of evidence approach (Annex XI, Section 1.2). In your justification for the following independent sources of information are presented:

i. Results from Pre-natal developmental toxicity study in rats (OECD TG 414)
ii. Results from Repeated dose toxicity study in rats (OECD TG 408)
iii. Gene expression profiling studying reproductive toxicity potential towards the developing testis.

Based on the presented lines of evidence you argue that the Substance is unlikely to be a reproductive toxicant and that there is sufficient information to support this notion.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance does or does not have a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow concluding on toxicity related to reproduction (sexual function and fertility and toxicity to offspring) for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an EOGRT study with the test design as requested in this decision:

- ten weeks premating exposure duration for the parental (P0) generation;

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

- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity); and
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning).

ECHA has assessed to what extent the information submitted enables a conclusion on hazardous properties for reproduction and identified the following deficiencies:

'Sexual function and fertility'

a. No Information on sexual function and fertility of the F1 generation

Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) similar to extension of Cohort 1B (i.e. mating of Cohort 1B animals to produce the F2 generation) must be provided because the criteria at Annex X section 8.7.3 column 2 are met.

You have not provided any source of information on 'sexual function and fertility' in the F1 generation.

'Toxicity to offspring'

b. No Information on toxicity to the offspring up to the adulthood

Information on toxicity to the offspring (Cohort 1A) after exposure from in utero, peri- and postnatal periods up to adulthood as foreseen to be investigated in OECD TG 443.

You have not provided any source of information on toxicity to offspring up to adulthood as foreseen to be investigated in OECD TG 443.

c. Exposure and information does not cover all relevant life stages as examined in OECD TG 443

Exposure must cover all the life stages foreseen to be investigated in OECD TG 443 as specifed in the request.

The OECD TG 414 study (i) investigates effects due to exposure during gestation (*in utero*). The OECD TG 408 study (ii) provides information on exposure on adult animals but only on organs, not for functional fertility. However, none of the available studies investigate 'the toxicity to the offspring' with regard to post-natal investigations of the F1 generation up to adulthood.

In conclusion, none of the sources of information alone or combined allows to conclude whether the Substance does or does not have hazardous properties related to 'sexual function and fertility' or 'developmental toxicity' to offspring.

In your comments on the draft decision, you indicate that you intend to create a category approach with all (or at least the majority of) REACH registered Trimellitates to have a greater pool of data. The update will include new information on the composition of the substances and additional data on toxicokinetics, mammalian toxicity, biodegradability, bioaccumulation and environmental toxicity on the category members which have been generated in the context of other regulatory obligations.

ECHA acknowledge your intention to develop a the read-across approach. However, without further details on the composition of the Substances intended to be included in the category; detailed results of the additional studies; and the improved read-across justification, ECHA is unable to assess whether the approach would comply with the Annex XI, Section 1.5. requiremnts of REACH.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

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[7]. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance (logKow > 4.5) to ensure that the steady state in parental animals has been reached before mating.

In your comments on the draft decision, you argue that the substance have a low bioaccumulation factor (19.3 L/kg wet weight) and that the toxicokinetic infromation on the substance give no hints of very slow clearance. Based on this you argue that there are no indications of that the substance reaches steady state only after extended exposure.

You have not provided any Substance-specific toxicokinetic infromation in your dossier or in your comments on the draft decision. The dossier contains theoretical considerations with regard toxicokinetics and toxicokinetic infromation based on read-across. As the read-across approach has been rejected toxicokinetic information on other substances are not relevant for the prediction of the toxicokinetic behavior of the Substance.

In addition, the logKow of the substance is 12.3 at 20°C well above the theshold for lipophilicity indicated in the ECHA Guidance. This means, that the substance will reach steady state only after extended exposure.

On this basis, the requested premating exposure duration is ten weeks.

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.

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

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

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

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

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of Section 8.7.3., Annex X) and

- there are indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of Section 8.7.3., Annex X).

The use of the Substance is leading to significant exposure of consumers and professionals because the Substance is used by professionals in lubricants and adhesives and inks (PROCs include 8b, 9, 10, 11) and consumers in lubricants and adhesives.

In your comments on the draft decision, you confirm that the Substance have significant exposure to professionals and consumers.

In your comments on the draft decision, you argue that there are no indications based on the available studies that endocrine disruption is a relevant mode of action, additionally no structural alerts exists.

There are indications of one or more modes of action related to endocrine disruption because changes in genes expression have been observed when rats are exposed to the Substance. In a specific mechanistic study ([redacted] 2010), changes in gene expression of the Substance with that of Bis(2-ethylhexyl) phthalate, EC No. 204-211-0 (CAS No. 117-81-7; DEHP) were compared. Male rats were exposed *in utero* by oral gavage of the dams (500 mg/kg/day; gestational days 12-19) and transcriptional profiling analysis of RNA extracted from neonatal testes. 564 and 3406 gene expression changes ($p<0.01$), relative to control, were caused by DEHP and the Substance, respectively. DEHP treatment caused bias in the gene list towards effects in the pathways of steroidogenesis and steroid metabolism. In contrast, the Substance gene list showed a bias towards effects on the pathways of hepatic stellate cell activation, glucocorticoid signalling, integrin signalling, androgen signalling and MAPK signalling. ECHA conclude that under the condition of the study the mode-of-action the Substance appears to differ from that of the known anti-androgen mode-of-action caused by the phthalate DEHP. The results show indications of other modes of action related to endocrine disruption caused by the Substance because of the bias in the gene lists towards genes involved in glucocorticoid signalling and androgen signalling.

With regard to your comments on structural alerts, ECHA notes that structural alerts are not scientifically valid (Q)SAR models, and therefore the results from these Profilers cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, Section 1.3 of REACH. QSAR Toolbox Profilers and structural alerts can be used to identify analogue substances and apply the grouping and read-across approach if the conditions under Annex XI, section 1.5. are fulfilled.

On this basis, Cohort 1B must be extended.

The F2 generation shall be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring.

Species and route selection

The study must be performed in rats with oral[8] administration.

Further expansion of the study design

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of 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 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[9].

[8] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[9] ECHA Guidance R.7a, Section R.7.6.

Appendix E: Procedural history

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.

The compliance check was initiated on 6 September 2018.

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 F: Observations and technical guidance

- This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

- 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 the Member States.

- 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 shall 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'[10].

- Test material

  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 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.

  Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[11].

[10] https://echa.europa.eu/practical-guides
[11] https://echa.europa.eu/manuals

- List of references of the ECHA Guidance and other guidance/ reference documents[12]

  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 in this decision.

  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)[13]

  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.

  OECD Guidance documents[14]
  Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
  Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No43, referred to as OECD GD43.

[12] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[13] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix G: 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]

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.