EUROPEAN CHEMICALS AGENCY

Helsinki, 14 August 2020

Addressees
Registrant(s) of JS-IPC-269-052-1 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
09/10/2019

Registered substance subject to this decision ("the Substance")
Substance name: Chrome antimony titanium buff rutile
EC number: 269-052-1
CAS number: 68186-90-3

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by ***22 May 2023***.

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

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

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

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, 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;

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

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

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

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

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 A: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study 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 the following information:

a) *Column 2 adaptation (Annex X, Section 8.7.)*

- In the dossier you have provided an adaptation claiming that "*the study does not need to be conducted because the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*".

b) Read-across adaptation (Annex XI, Section 1.5.)

- In your comments to the draft decision you have also expressed your intention to adapt this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. proposing to perform an OECD TG 414 guideline study in rabbits via the oral route with the analogue substance (Antimony nickel titanium oxide yellow (Pigment Yellow 53), EC no. 232-353-3).

We have assessed this information and identified the following issues:

You have not provided information on a second species. In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

a) *Column 2 adaptation (Annex X, Section 8.7.)*

According to Annex X, Section 8.7., Column 2, third indent, the study does not need to be conducted if three concomitant criteria are fulfilled, one of them being that there is no or no significant human exposure.

In your registration dossier, the description of the uses of the Substance indicate that there is human exposure. More specifically, you reported:

- During manufacture and formulation (ceramics, paints and coatings), PROCs 8b, 9, 14;
- For professional uses, PROCs 5, 8a, 8b, 10, 11, 13, 19, 24,

which all suggest significant human exposure. You have not provided additional data to demonstrate the contrary, nor have you submitted information regarding the use by consumers of products containing the substance.

To conclude you have not demonstrated the absence of significant human exposure and hence your adaptation is rejected.

b) Read-across adaptation (Annex XI, Section 1.5.)

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.

You have provided a read-across justification in your comments to the draft decision for this information requirement.

You predict the properties of the Substance from the structurally similar substance: Antimony nickel titanium oxide yellow (Pigment Yellow 53), EC no. 232-353-3. (i.e. the source substance).

The source study that you propose to use in your read-across approach, is a PNDT study in rabbits (OECD TG 414).

You have provided the following reasoning for the prediction of toxicological properties:
- *"Both, target as well as source substance, share high similarity in structure."*
- *The solubility of the target and source substances in water is very low [...] Bioavailability is regarded as negligible for both [...]"*
- *"The overall toxicological profile is virtually identical as demonstrated amongst many other studies by two OECD 414 studies in rat which yielded the very same results (no toxicity up to the limit dose [...]."*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regards to the predictions of toxicological properties:

(i.) Read-across hypothesis

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[2]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and toxicological properties between the source substance and your Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

Similarity in chemical structure and similarity of some of the physicochemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. As described above, a well-founded hypothesis is needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance and your Substance.

(ii.) Relevance of the supporting information

[2] Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals.

According to the ECHA Guidance[3] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance(s) have similar properties for the developmental toxicity endpoint in the read-across approach, you refer to their repeated dose toxicity properties but also to the developmental toxicity properties in rats.

Whilst this data set suggests that the substances may have similar properties for repeated dose toxicity and developmental toxicity in rats, these studies do not inform on the developmental toxicity properties of the target and source substances in rabbits. You did not consider how this species difference could influence the prediction from the source substance to the Substance.

Accordingly, these information are not considered as relevant to support prediction of this information requirement.

(iii.) Missing information on the impact of non-common compounds

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*"[4]. 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 the source substance(s).

Supporting information must include supporting information on the formation of non-common compound.

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

In your read-across justification you only refer to the the low water solubility and negligible bioavailability of the target and source substances and the lack of effects observed in the PNDT studies in rats with both substances. Only results from bioaccessibility studies are provided, showing some release of Ni and Cr, with a limited observation/measurement time of maximum 24 hours.

You did not provide sufficient information characterising the exposure to the non-common compounds resulting from exposure to the Substance and of the source substance(s). No experimental data or other adequate and reliable information addressing the impact of exposure to these non-common compounds is included in the documentation of your read-across approach. In the absence of such information, you have not established that a reliable

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

(iv.) Conclusions on the read-across approach

With reference to your comments to the draft decision, ECHA acknowledges your intention to update the dossier with a read-across justification for this information requirement. However, as explained above, currently 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.

Based on the above, the information you provided does not fulfil the information requirement.

Information on study design

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

The study must be performed in rabbits with oral[5] administration of the Substance.

2. Extended one-generation reproductive toxicity study

An Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement in Annex X to the REACH Regulation.

You provided the following adaptation *"A screening study (acc. OECD 422) was without relevant findings up to the limit dose of 1000 mg/kg bw/d. No effects were observed on mating behaviour, reproductive organs and fertility.In addition, no histopathological changes were observed in the gonads following 90 day repeated administration of the test material which suggests that effects on fertility are unlikely ([redacted] 2003; [redacted], 2003). A recent publication which included a meta-analysis of more than 100 90-day studies came to the conclusion that the NOAELs from these studies differed by no more than the variation limit of the corresponding NOAEL from 2-generation studies with the same test material, i.e. there would be no additional value from a further 2-generation study if a 90-day study has been performed ([redacted] 2007). This is especially relevant in view of the low bioavailability and absence of systemic effects (endocrine effects, immnuotoxicity, neurotoxicity) in repeated dose studies with this class of substances."*

While you did not indicate a specific adaptation , ECHA has evaluated the information you provided according to Annex XI, Section 1.2 of REACH (weight of evidence).

In support of your adaptation, ECHA understands that you refer to the following sources of information:

(i) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 ([redacted] 2002);
(ii) Sub-chronic repeated dose toxicity study similar to OECD TG 408 ([redacted] 1982);
(iii) Several scientific publications from the open literature ([redacted] 2003, [redacted]

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

2003, [redacted] 2007).

While not explicitly mentioned in your justification, ECHA understands that the statement "*no histopathological changes were observed in the gonads following 90 day repeated administration*" refers to source of information (ii) which is included in the registration dossier.

Based on these sources of information, you argue that the available data gives sufficient information to conclude on the reproductive toxicity.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, relevance and completeness of the information for the given regulatory information requirement. Subsequently, relevance, reliability, completeness, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not included a documented justification for your weight of evidence adaptation explaining why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".
Regarding source of information (iii) you have not provided robust summaries for any of these scientific publications referred to in your adaptation. Neither have you explained on which substance these studies were performed.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Any relevant information that can be used to support a weight of evidence adaptation for the information requirement of Section 8.7.3 at Annex X must include similar information to that produced by the OECD TG 443 design. At a general level, the sources must cover information on 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

Sexual function and fertility

On a more specific level, a study according to OECD TG 443 investigates "sexual function and fertility" on both sexes including information on mating, fertility, gestation, parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The sources of information (i. and ii.) provide relevant information on sexual function and fertility in parental P0 animals, although source (ii.) informs only on organ weights and histopathology of reproductive organs. As mentioned above there is no documentation for the source publications (iii.) but ECHA understands that these publications discuss the usefulness of histopathological data from reproductive organs in assessment of reproductive toxicity and could be of relevance. However, the following deficiencies affect the reliability of the sources of information with a view to verifying the accuracy of conclusions from these sources of information.

Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) must be investigated in parental P0 animals as indicated in OECD TG 443 after *at least ten weeks premating exposure* duration if extension of Cohort 1B is not included[6]. In the case of your Substance, the conditions to include the extension of Cohort 1B are currently not met, because the Column 2 specific rules for adaptation under REACH Annex IX Section 8.7.3. are not fulfilled.

The source of information (i.) investigates sexual function and fertility with the premating exposure duration of two weeks for the parental P0 animals. The other source (ii.) does not have any premating exposure.

Neither of the sources of information (i.) and (ii.) thus investigate the sexual function and fertility in the P0 generation with sufficient premating exposure duration to ensure the coverage of full spermatogenesis and folliculogenesis before mating.

Additionally, the information must be derived from the Substance or from acceptable read-across source substance(s). The source publications (iii.) do not present information on the Substance. You have not provided any justification why and how information from source publications (iii.) can inform on sexual function and fertility of the Substance, i.e. there is no read-across justification available.

In the comments you provided on the draft decision, you expressed your intention to cover the required information by providing information from the studies OECD TG 408 (ii), OECD TG 422 (i) and OECD TG 414 (in two species). You consider that the OECD TG 422 (i) informs on mating, fertility, gestation, parturition, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity and litter sizes. OECD TG 408 (ii) informs on histopathology of the reproductive organs after 3 months oral exposure. OECD TG 414 informs on conception rate, implantation sites and potential pre- and post-implantation losses. You aim also to include supporting information (iii) to demonstrate the relevance of sub-chronic (histopathological) data for (male) fertility and added value of the generation study regarding NOAEL. We note the following deficiencies in your proposal:

- Your proposal does not cover the impact of 10 weeks premating exposure duration for sexual function and fertility, especially on functional fertility as investigated in information requirement.
- OECD TG 414 suggests dosing of the females, daily from implantation i.e. day 5 post mating, therefore no treatment related information on the conception rate and pre-implantation loss can be drawn from this study. OECD TG 414 provides only limited information for sexual function and fertility in form of maintenance of pregnancy.
- For the supporting information from publications (iii), focusing on sensitivity of male testis histopathology and added value of two-generation study for NOAEL selection, you do not explain why and how this information can inform the properties of your Substance – there is no read-across justification available. You have also not explained why and how, following suggestion from these publications (iii), information from a sub-chronic toxicity study (ii), would reliably and sufficiently predict the outcome from investigations included an OECD TG 443 in both sexes regarding both the risk

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

assessment and hazard classification for your substance.

- Information from reproduction toxicity studies is used not only for risk assessment to identify the most sensitive parameter and NOAEL values but also for hazard identification to inform on hazard classification which is not dependent only on the most sensitive effects but takes into account all effects related to the information requirement and reflects the intrinsic properties of a substance.

In the absence of reliable information in your dossier as well as your comments on the sexual function and fertility after exposure to the Substance over a pre-mating period of 10 weeks, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

Toxicity to the offspring

On a more specific level, a study according to OECD TG 443 further investigates "toxicity to offspring" including information on deaths before, during or after birth, growth, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

You have only provided one relevant source of information (i.), and it only provides some information on toxicity to the offspring up to post-natal day 4.

Information provided on toxicity to offspring is limited and does not cover all relevant and essential aspects as defined above. The source of information (i.) does not inform on toxicity to the offspring up to adulthood. Therefore, information on toxicity to offspring is not complete and no conclusion can be drawn on toxicity to the offspring as required by the information requirement.

In the comments you provided on the draft decision, you indicated that the above information will be provided by means of the OECD TG 414 studies (in two species), in particular for litter size and foetus weight, number of live offspring, sex ratio and external, soft tissue and skeletal malformations. The additional points i.e. growth, sexual maturity and adulthood of the offspring you aim to cover by the scientific publications (iii; [redacted] 2003, [redacted] 2003, and [redacted] 2007). We note the following deficiencies in your proposal:

- Results from OECD TG 414 studies only provide information on toxicity to the foetuses and do not inform on toxicity to the offspring up to adulthood.
- The scientific publications (iii) intended to provide information on growth, sexual maturity and adulthood in the offspring, do not contain information on the Substance and there is no read-across justification available to explain why and how this information is related to the properties of the Substance. Furthermore, these publications focus on relevance of sub-chronic toxicity studies in predicting male gonad toxicity and comparing the NOAEL values between studies. They do not address the toxicity to the offspring including information on deaths before, during or after birth, growth, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

None of the sources of information does inform on toxicity to the offspring up to adulthood. Therefore, information on toxicity to offspring is not covered and no conclusion can be drawn on toxicity to the offspring as required by the information requirement.

Systemic toxicity

On a more specific level, a study according to OECD TG 443 further investigates "systemic toxicity" including information on clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive

organs and other potential aspects of systemic toxicity in both the parental and F1 generations.

The sources of information (i.) and (ii.) inform on systemic toxicity, especially haematology, clinical chemistry and organ weight and histopathology of non-reproductive organs from 5 and 15 P0 parental animals/sex/group (source i. and ii. respectively).

However, it does not cover all relevant and essential aspects as defined above. In particular, there is no information on systemic toxicity from F1 generation, such as clinical signs, body weights, haematology, clinical chemistry, organs weights and histopathology of non-reproductive organs in adulthood. Therefore, the information on systemic toxicity is not complete and no conclusions on the systemic toxicity and its relationship with reproductive toxicity can be made.

In the comments you provided on the draft decision, you indicated your intention to cover the information on systemic toxicity in parental and F1 generations by providing information from the studies OECD TG 408, OECD TG 422 and the *in vitro* bioaccessibility assays. You consider that the subacute as well the sub-chronic study provides "*sufficient information on clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organs weights and histopathology of non-reproductive organs and show clearly the absence of toxicological effects in parental animals and offspring even at limit dose concentrations.*" Bioaccessibility studies will demonstrate, according to you, the very limited systemic availability of the test item.

We note the following deficiencies in your proposal. There is no information available to inform on systemic toxicity in F1 generation, such as clinical signs, body weights, haematology, clinical chemistry, organs weights and histopathology of non-reproductive organs in adulthood. Therefore, the information on systemic toxicity in F1 generation is not covered and no conclusions on the systemic toxicity in F1 generation and its relationship with reproductive toxicity can be made.

Conclusion

Taken together, the sources of information as indicated above, provide relevant information on the sexual function and fertility of the Substance on parental P0 generation but its reliability is affected by a lack of sufficient premating exposure and the limited number of animals. There is relevant, but incomplete information provided for toxicity to offspring and systemic toxicity, lacking information on relevant life stages of the F1 generation (post-natal period up to adulthood). Therefore, a significant amount of essential information is lacking that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity in order to conclude on these aspects.

In your comments to the draft decision, you aim to improve the documentation for weight of evidence justification, include and link the scientific publications (iii) to the adaptation, include bioaccessibility studies to demonstrate the very limited systemic availability of the test item. Furthermore you propose an interim update of your weight of evidence adaptation after completion of the OECD TG 414 study in rabbits to demonstrate the validity of your adaptation.

We note that there is still a significant amount of essential information lacking that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity in order to conclude on these aspects. Especially, the relevant information on toxicity to offspring and and systemic toxicity from post-natal period up to adulthood in F1 generation is missing and the reliability of information on sexual function and fertility without the 10 weeks premating exposure duration is not addressed.

You furthermore aim to provide an exposure assessment for workers and consumers to demonstrate the safe use and the absence of a risk for human health while handling.

However, a weight of evidence adaptation is hazard based and focusing on intrinsic properties of the substance and exposure-related justifications are irrelevant in context of this adaptation.

It is not possible to conclude, based on any source of information alone or considered together, including your comments to the draft decision, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided does not fulfil the information requirement.

We provide below 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 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.[5]

Therefore, the requested premating exposure duration is ten weeks.

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.

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.

Species and route selection

The study must be performed in rats with oral[7] administration with the Substance.

Cohorts 1A and 1B

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

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/or 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

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

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[8].

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

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[9].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. *Selection of the Test material(s)*
   The Test Material used to generate the new data must be selected taking into account the following:

   a) the variation in compositions reported by all members of the joint submission,
   b) the boundary composition(s) of the Substance,
   c) the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. *Information on the Test Material needed in the updated dossier*
   a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[10].

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

Appendix C: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 01 July 2019.

ECHA notified you of the draft decision and invited you to provide comments

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

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: List of references - ECHA Guidance[11] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[13]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

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

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.