Helsinki, 20 February 2019

Addressee: [redacted]

Decision number: TPE-D-2114460726-43-01/F
Substance name: Tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate
EC number: 250-418-4
CAS number: 30989-05-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17/12/2015
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **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:**
   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity).**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **27 August 2021**. You also have to update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

ECHA
EUROPEAN CHEMICALS AGENCY

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.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment C4

[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 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you.

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation.

If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 443 in rats by the oral route to be performed with the registered substance with the following justification and specification of the study design: *"The study will be performed in rats according to OECD guideline 443 in compliance with GLP. The test substance will be administered by the oral route. The basic configuration of EOGRTS will be performed as based on the toxicological profile of the substance there are no concern-driven scientific triggers for the performance of the F2 generation (extension of Cohort 1B), developmental neurotoxicity (DNT; cohorts 2A and 2B) and/or developmental immunotoxicity (DIT; cohort 3) cohorts. For instance, there are no indications from existing in vivo studies that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, there are no indications of one or more relevant modes of action related to endocrine disruption from available data, and the available OECD 408 study gave neither indications for neurotoxicity nor immunotoxicity. The highest dose level will be selected in agreement with the testing laboratory and study director with the aim to induce some toxicity, in order to allow a conclusion on whether potential effects on reproduction are considered to be secondary, non-specific consequence of other toxic effects seen. The study will only be performed if really needed, based on the scientific and regulatory evolutions at the time of the ECHA decision on the testing proposal."*

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA also notes that adverse effects on reproductive organs (testes and epididymides)

were observed in the provided 90-day repeated dose toxicity study according to OECD TG 408 with the registered substance indicating a concern for reproductive toxicity.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of Section 8.7.3., Annex X is required.

In your comments on the draft decision, you have indicated your willingness to conduct the extended one-generation reproductive toxicity study.
You further referred to animal welfare reasons in your justifications for not including the extension of Cohort 1B as well as the DNT and DIT cohorts in the study. Independently of animal-welfare considerations, as the triggers defined in the legal text for extension of Cohort 1B and inclusion of Cohorts 2A/2B and 3 are met, the full blown study design must be conducted as explained below.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You did not propose the length of the premating exposure duration.

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should 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 on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

With respect to dose-level setting you stated that "*The highest dose level will be selected in agreement with the testing laboratory and study director with the aim to induce some toxicity, in order to allow a conclusion on whether potential effects on reproduction are considered to be secondary, non-specific consequence of other toxic effects seen.*"

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 with the other cohorts being tested at the same dose levels.

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. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed to not extend Cohort 1B to the F2 generation because "*there are no concern-driven scientific triggers for the performance of the F2 generation (extension of Cohort 1B)... For instance, there are no indications from existing in vivo studies that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, there are no indications of one or more relevant modes of action related to endocrine disruption from available data ...*".

In line with column 2 conditions of 8.7.3., Annex X, the use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by professionals (PROCs 8a and 9) and consumers as lubricants, lubricant aditives, pressure transfer agents and brake fluid.

Furthermore, in line with column 2 conditions of 8.7.3., Annex X, there are indications for endocrine-disrupting modes of action in an *in vivo* study on intact animals (*i.e.* the 90-day repeated-dose toxicity study in rats by oral route according to OECD TG 408 with the registered substance at 10, 100 and 1000 mg/kg bw/day corresponding to 0.22, 2.16 and 21.6 mg boron/kg bw/day, respectively) because changes in testes and epididymides have been observed: "*Two males treated with 1000 mg/kg bw/day* [equivalent to 21.6 mg boron/kg bw/day] *had small and flaccid testes. One of these males also had small epididymides. A further male treated with 1000 mg/kg bw/day had a small left testis. One male treated with 10 mg/kg bw/day* [equivalent to 0.216 mg boron/kg bw/day] *had small testes and another male from this treatment group had a small right testis.*"

You disregarded these findings because "*In the absence of any treatment related histology correlates the intergroup differences were considered not to be of toxicological importance.*"

However, ECHA does not agree with your conclusion that these findings have no toxicological importance for the following reasons:

a) ECHA notes that it is an inherent property of the registered substance to hydrolyse rapidly to borate (hydrolysis half-life < 10 minutes at pH values of 1.4, 4, 7 and 9 as recorded in the registration dossier) and, therefore, also information on borate is considered relevant.

b) It is well established that exposure to borate leads to boron-mediated testicular atrophy as for example noted in rats in a 90-day repeated-dose toxicity study at 88 mg boron/kg bw/d and at lower incidence also at 26 mg boron/kg bw/d (see for example the ECHA Annex XV dossier[2] for boric acid or the EPA Toxicological review of boron and compounds[3]). These findings are consistent with the small testes findings at doses up to 21.6 mg boron/kg bw/day observed in the 90-day study with the registered substance.

[2] https://echa.europa.eu/documents/10162/13640/svhc_axvrep_germany_cmr_boric_acid_en.pdf
[3] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0410tr.pdf

ECHA notes that the vehicle used in the OECD TG 408 study is ethanol, 2-[2-(2-methoxyethoxy)ethoxy] (TGME) which by itself may cause testicular toxicity at high concentrations. This is explained in the OECD SIDS report for TGME which is attached to the OECD TG 408 endpoint study record in the registration dossier: "*Male rats orally administered 4,000 mg/kg/day TGME for 91 days exhibited testicular toxicity characterized by mild to moderate degeneration and/or minimal to moderate atrophy of the seminiferous tubules (spermatocytes or developing spermatids). In the same study, testicular toxicity was observed in 1/15 males at 1200 mg/kg/day and no testicular effects were noted at 400 mg/kg/day. Similarly, a 91-day repeated-dose dermal toxicity study in rats given 400, 1,200 or 4,000 mg TGME/kg/day showed severe testicular toxicity in 1/10 animals given 4,000 mg/kg/day and minimal decreases in developing germ cells in 1/10 rats given 1,200 mg/kg/day. No testicular effects were seen at 400 mg/kg/day. The NOAELs for reproductive toxicity determined from both the oral and dermal studies are between 400 and 1200 mg/kg/day.*"

Because both the hydrolysis product of the registered substance and the used vehicle can cause testicular toxicity, it is not possible to conclude with certainty that the observed effects are due to exposure to the registered substance, the vehicle or both. However, and as explained above, because the registered substance hydrolyses rapidly to borate which is known to cause testicular toxicity, there is a particular concern for the registered substance to cause testicular toxicity.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there are indications of modes of action relevant to endocrine disruption for the registered substance.

In your comments on the draft decision, you do not agree with the request for extending Cohort 1B to produce F2 because the findings used for triggering are toxicologically not relevant: Small testes are occasionally seen in untreated rats and there were no dose-response relationship or histopathological correlates. You also consider that (i) the F1 generation already addresses the identified concern, (ii) endocrine effects of borate are secondary and do not induce tumours, (iii) boric acid does not exert oestrogenic effects and, has no structural similarity to known oestrogenic-active substances, it received a low score in the US EPA ToxCast programme, and (iv) no hormonally-related symptoms have been described in workers.

The registered substance hydrolyses quickly to borate which exerts testicular toxicity. Therefore, the concern is not removed by the finding that macroscopic small testes are also occasionally seen in un-treated young and old male Wistar rats from 4-, 13-, and 26-week studies.
Even though there is no dose-response relationship, similar effects were seen in 3 males in the high-dose group and in 2 males in the low-dose group; *i.e.* the number of animals for which the effect was observed increased from low- to high-dose group. The absence of testicular effects in the mid-dose group may result from the low number of incidents.

ECHA acknowledges that no histopathological correlates were reported in the 90-day study. However, the absence of such correlates in this particular study does not remove the concern which is based on well-known testicular toxicity exerted by the hydrolysis product borate.

Furthermore, you state that a second generation is not necessary to investigate the concern

stemming from testicular toxicity and that investigations on F1 offspring suffice. However, ECHA considers that it is relevant to investigate both P0 parents/F1 offspring and F1 mating pairs/ F2 offspring to establish whether the effects are more prominent or with a broader/different spectrum in F1 mating pairs/ F2 offspring compared to P0 parents/ F1 offspring.
You explain that the testicular toxicity does not result from a mode of action related to endocrine disruption. ECHA emphasises that according to the legal text, already "*indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies*" are a sufficient trigger for the extension of Cohort 1B. ECHA also notes that the legal text does not specify whether the mode of action related to endocrine disruption must be primary or secondary. In this case, toxicity on the endocrine-active testes may result in relevant hormonal changes which then may exert additional toxicity.

Non-induction of tumours is not a sufficient criterion to exclude endocrine-modes of action. ECHA further notes that negative results in oestrogenicity tests and missing structural similarity with known oestrogenic substances do not exclude other endocrine-related mode of actions. Furthermore, negative *in vitro* tests or computational models do not remove the concern identified *in vivo*.

You also explain that "*No evidence of hormonally-related clinical symptoms has been reported in workers exposed to boric acid.*" However, no reference is given to assess the validity of this claim.

Finally you state that "*In general, there are sufficient scientific and regulatory reasons that the extension of Cohort 1B to mate the F1 animals to produce the F2 generation is not providing additional information regarding hazard evaluation including the purpose of classification and labelling*", thereby referring to publications by Piersma *et al.*, Martin *et al.*, Janer *et al.*, Beekhuijzen *et al.*, and Rorije *et al.* However, this reason and the referenced publications are not relevant. The REACH Regulation defines and ECHA Guidance explains that the extension of Cohort 1B to produce an F2 generation is required if specific requirements are met (see column 2 of 8.7.3., Annex X). In this specific case, this requirement is met as explained above. You do not explain how your reasoning and the referenced publications are relevant for the registered substance and how this information can be used for the registered substance to not trigger the extension of Cohort 1B.
ECHA maintains its position that extension of Cohort 1B to produce F2 is triggered and needs to be conducted.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B because "*... there are no concern-driven scientific triggers for ... developmental neurotoxicity (DNT; cohorts 2A and 2B) ... and the available OECD 408 study gave neither indications for neurotoxicity ...*".

ECHA notes that existing information on the registered substance itself derived from the available 90-day repeated-dose toxicity study show evidence of statistically significant reduction in mean hind limb grip strength and overall activity in males of all treatment groups, statistically significant reduction in overall mobility in males treated with 100 and 1000 mg/kg bw/day, statistically significant reduction in the final 20% of activity in males

treated with 10 mg/kg bw/day, and statistically significant reduction in mean fore limb grip strength in females treated with 100 and 1000 mg/kg bw/day, all in the absence of general toxicity.

According to ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017) "*any signs of behavioural or functional adverse effects on the nervous system in adult studies e.g. repeated-dose …, not likely to be secondary to general toxicity: clinical and/or behavioural signs if seen in absence of general toxicity*" are substance specific findings which indicate a particular concern justifying inclusion of the developmental neurotoxicity cohorts.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance.

In your comments on the draft decision, you do not agree that the observations from the 90-day repeated-dose toxicity study are sufficient to trigger the inclusion of Cohorts 2A and 2B because the observed changes in functional performance are considered not to be of toxicological relevance due to the absence of a true dose-related response and any supporting clinical observations that would indicate an effect of neurotoxicity. Furthermore, you explain that no corroborative histological changes in central or peripheral nervous system tissues were observed.

In ECHA's view, Table 1 (Group Mean Functional Performance Test Values) provided by you in your comments confirms the findings based on which the DNT Cohorts 2A and 2B are triggered.

According to ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017) "*any signs of behavioural or functional adverse effects on the nervous system in adult studies e.g. repeated-dose and acute toxicity studies and neurotoxicity studies, not likely to be secondary to general toxicity*", and in particular "*clinical and/or behavioural signs (such as abnormal gait, … or any other altered activity) if seen in absence of general toxicity*" indicate a particular concern justifying inclusion of the developmental neurotoxicity cohort. Additional clinical signs and histological changes in tissues of the central or peripheral nervous system are not needed to trigger the DNT Cohorts 2A and 2B. As explained above, behavioural signs alone, if seen in the absence of general toxicity, are sufficient to establish a particular concern for DNT.

ECHA considers that the above-mentioned findings are of toxicological relevance because they are statistically significant, severe and are seen in the absence of general toxicity. Therefore, ECHA does not agree with your comments that the findings are of no toxicological relevance, and are unlikely to be a result of the exposure to the registered substance.

ECHA maintains its opinion that the DNT Cohorts 2A and 2B need to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3 because "*… there are no concern-driven scientific triggers for … developmental immunotoxicity (DIT; cohort 3) … and the available OECD 408 study gave neither indications for … immunotoxicity …*".

ECHA notes that existing information on the registered substance itself derived from the available 90-day repeated-dose toxicity study show evidence of a statistically significant reduction in thymus weight, both absolute and relative to terminal body weight, in males treated with 1000 mg/kg bw/day, in the absence of general toxicity.

According to ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017) " *one severe ... statistically and/or biologically significant organ weight ... finding related to an immunology organ*" is a substance specific finding which indicates a particular concern justifying inclusion of the developmental neurotoxicity cohorts.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

In your comments on the draft decision, you do not agree with the inclusion of Cohort 3 because the decrease in thymus weight in high dose males was not associated with histopathology correlates; no further effects indicating immunotoxicity (e.g. no reduction in lymphocytes) were observed in the 90-day repeated-dose toxicity study; and according to the WHO Guidance for Immunotoxicity Risk Assessment for Chemicals, a decrease in thymus organ weight as sole immune-related finding is not a definitive indicator for immunotoxicity.

According to ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017) "*one severe (see footnote 43) statistically and/or biologically significant organ weight or histopathological finding related to an immunology organ, e.g. thymus atrophy*" indicates a particular concern justifying inclusion of the developmental immunotoxicity cohort.
Tables 2 (Group Mean Thymus Weights) and 3 (Individual and Group Mean Thymus Weights in Male Animals) provided in your comments confirm the findings based on which the DIT Cohort 3 is triggered.

The triggering of Cohort 3 is based on a statistically significant reduction in thymus weight observed in this study, both absolute (-19.4%) and relative to terminal body weight (-23.1%), in males treated with 1000 mg/kg bw/day, in the absence of general toxicity. ECHA further notes that there is a tendency to lower mean thymus weights also in the low- and mid-dose groups compared to controls.

Histopathological correlates and further effects indicating immunotoxicity are not needed to trigger the DIT Cohort 3. ECHA applies the criteria of the ECHA Guidance when considering the study design of the EOGRTS. In this respect, the WHO Guidance has no regulatory relevance for ECHA.

As explained above, *one severe statistically and/or biologically significant organ weight finding related to an immunology organ (i.e. the thymus)* alone is sufficient to establish a particular concern for DIT.

ECHA maintains its opinion that the DIT Cohort 3 needs to be conducted.

Species and route selection

You proposed testing in rats. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the oral route. ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) extension of Cohort 1B, 3) termination time for F2 generation, and 4) inclusion of Cohorts 2A/2B and 3.

Notes for your considerations

After a Proposal for Amendment by a Member State competent authority, ECHA considers that no excessive toxicity occurred in animals up to the limit dose of 1000 mg/kg bw/day in the prenatal developmental toxicity and sub-chronic toxicity studies provided in the registration dossier. Therefore, the limit dose as used in these studies is recommended to also be used in the extended one-generation reproductive toxicity study unless new information becomes available that indicates that a dose of 1000 mg/kg bw/day will result in excessive general toxicity. If the limit dose would result in excessive toxicity, the highest dose level should be chosen with the aim to induce systemic toxicity, but not death or severe suffering of the animals.

In your comments to the Proposal for Amendment, you indicated (1) that based on the prenatal developmental effects seen in rat and rabbit studies, there is excessive toxicity (possibly "incalculable suffering" of F1 animals at limit dose). ECHA notes that the rabbit study is not directly relevant for dose-setting for an EOGRT study, which would be performed in rats. ECHA has examined the information provided in the rat PNDT study, and considers that no excessive toxicity occurred in this study, either for the adults or the fetuses. (2) that there is an inadequate basis for setting the correct dose for an EOGRT study and that a dose-range finding study may be necessary. ECHA agrees that it is your responsibility to set the dose levels in line with our requirements, and to determine if further studies are needed to set the dose levels in line with our requirements.

Extension of the deadline

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the deadline by 18 months to 42 months, due to e.g. laboratory capacity and additional formulation experiments needed.

You sought to justify this request, based on a statement of your laboratory *"taking into account that the test item is unstable and [...] considering the complexity of the requested study and [...] the request of a second generation, [...] a further time period of 24 months is scheduled for the definitive study."*
ECHA considered your request and the provided evidence. However, an 18-month extension seems excessive.
ECHA considers that lab capacities are currently sufficient to schedule the requested extended one-generation reproductive toxicity study without significant delay. Furthermore, contract laboratories could be already inquired now. However, ECHA acknowledges that the OECD TG 443 is a rather new guideline; that experience with this study might be still limited; and that additional formulation finding and stability experiments are needed. Therefore, ECHA has extended the deadline to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 9 December 2016.

ECHA held a third party consultation for the testing proposals from 29 April 2016 until 13 June 2016. ECHA did not receive information from third parties.

This decision does not take into account any updates after **30 May 2018**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-63 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

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 the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.