EUROPEAN CHEMICALS AGENCY

Helsinki, 18 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114382257-43-01/F
Substance name: BORON ORTHOPHOSPHATE
EC number: 236-337-7
CAS number: 13308-51-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15 July 2016
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Description of the analytical methods (Annex VI, Section 2.3.7.) for the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56. / 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 some 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;**

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 of the REACH Regulation. In order 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. In particular, you should consider the possibility to classify the registered substance as toxic for reproduction category 1B in accordance with the criteria established in Regulation (EC) No 1272/2008 to adapt the requirement for the extended one-generation reproductive toxicity study based on the Annex IX, section 8.7, column 2.

In case you decide to adapt the request for the extended one-generation reproductive toxicity study, you are required to submit the adaptation, self-classification and the description of analytical methods in an updated dossier by **26 March 2018**. In case you decide to conduct the extended one-generation reproductive toxicity study, you are required to submit all requested information in an updated registration dossier by **25 December 2019**. You shall also update the chemical safety report, where relevant.

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

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, shall 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, Evaluation E3

[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

1. Description of the analytical methods (Annex VI, Section 2.3.7.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

According to Annex VI, section 2.3.7. of the REACH Regulation, a registration dossier shall report a description of the analytical methods or the appropriate bibliographic references for the identification of the substance and where appropriate for the identification of impurities and additives. The reporting shall be given in sufficient detail that the methods may be reproduced.

You have included analytical data in reports "[redacted]" attached to section 1.4 for the identification and quantification of the main constituent [redacted] reported in the composition record in section 1.2.

The compositional information reported in section 1.2 cannot be verified as the description of the methods used to identify and quantify your substance composition is insufficiently reported in section 1.4 of your dossier. No analytical data for the identification or quantification of the impurity [redacted] is reported in your legal entity composition record of the technical registration dossier.

You are accordingly requested to provide a description of the quantitative analytical method(s) to identify and quantify the [redacted] impurity reported in section 1.2. The description of the method(s) shall be given in such detail that the method(s) may be reproduced and shall include details of the experimental protocol, any calculations made and the results obtained. The information shall be sufficient to enable the impurity information reported in section 1.2 of your dossier to be verified.

Technical instruction on how to report the requested information: The information shall be attached to section 1.4 of your dossier.

In the comments to the draft decision the Registrant agreed with the information requirement in the draft decision. In addition, he indicated his intention to address the information requirement in an update of the registration.

The Registrant outlined in the comments to the draft decision how he could address the information requirement by stating that "we he have already commissioned analytical studies to describe the composition of our boron orthophosphate products in such a detail that the [redacted] impurity can be quantified. The Final Report of this analytical analysis (incl. manufacturing methods and the assurance of our product quality (impurity of [redacted] will never exceed the reported quantity in our dossier) will be available in the next weeks."

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following:

The Registrant is reminded that this decision does not take into account any updates submitted after date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with 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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.
If the conditions described in column 2 of Annex IX 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 R.7a, chapter R.7.6 (version 4.1, October 2015).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

ECHA considers that in the only available repeated dose toxicity study, namely the sub-chronic toxicity study in mice, no adverse effects on reproductive organs or tissues are observed. However, there is existing information on (bio)transformation products of the substance subject to the present decision that triggers the EOGRTS at Annex IX because testicular atrophy was observed in the rat as the more sensitive species. In this respect, ECHA emphasises that (bio)transformation pathways are considered an intrinsic property of the substance being evaluated, inevitably resulting in the formation of certain (bio)transformation products, which can exert relevant effects for triggering.[2]

In particular, ECHA considers that the registered substance contains an impurity in the form of boric acid up to [redacted]% and also, the registered substance is claimed to be a subject to hydrolysis forming boric acid and borate species in water: *"An experimental study on hydrolysis as a function of pH is not available for Boron orthophosphate (CAS 13308-51-5).*

[2] See ECHA's scientific report on EOGRTS which is available in the Internet at https://echa.europa.eu/documents/10162/13630/eogrts_design_en.pdf/09123723-1df7-43cd-952b-21eb365a5d2c

Basically Boron orthophosphate is subject to hydrolysis in water forming boric species and hydrogen phosphate species under environmental pH, when release to water. The chemical form of boron found in water is dictated by pH and other constituents (Sprague 1972). In natural waters, boron forms stable species and exists primarily as undissociated boric acid [B(OH)3] and complex polyanions (e. g., B(OH)4-) (Howe, 1998). These forms of boron are highly soluble and not easily removed from solution by natural mechanisms. Borate and boric acid are in equilibrium depending on the pH of the water. At an acidic pH, boron exists in solution mainly as undissociated boric acid, whereas at alkaline pH it is present as borate ions (Howe, 1998)." ECHA notes that boric acid and borates are known to pose a serious concern for reproductive toxicity due to the boron-mediated severe testicular effects and are therefore classified as Repr 1B (H360F). Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

You did not consider the information requirement for reproductive toxicity in Annex IX, Section 8.7.3., column 1, because no adverse effects on reproductive organs or tissues have been observed in the only repeated dose toxicity study provided in the registration dossier and this study did not reveal other concerns in relation with reproductive toxicity: *"In accordance with Regulation (EC) No 1907/2006, Annex IX, 8.7.3, Column I, an extended one-generation reproductive toxicity study (OECD 443) is required in one species, using the most appropriate route of administration and having regard to the likely route of human exposure, if the available repeated dose toxicity studies (e.g. 28-day or 90- day studies, OECD 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxic. For boron orthophosphate (CAS 13308-51-5) a 90-day repeated dose toxicity study in mice via the oral route was performed ([redacted] 2016). No adverse effects on reproductive organs and tissues such as ovaries, oviducts, uterus, vagina, epididymis, prostate, seminal vesicle, coagulating gland and testes up to and including the highest dose level of 1000 mg/kg bw/day were observed. No concerns in relation with reproductive toxicity were noted. Also, a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats via the oral route following OECD 422 with boron orthophosphate will be commissioned by the registrant. Moreover, a pre-natal developmental toxicity study via the oral route according to OECD 414 for boron orthophosphate is proposed. It is suggested to await the outcome of the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) and to decide afterwards how to proceed with an extended one-gene ration reproductive toxicity study. Therefore, according to Regulation (EC) No 1907/2006 and with respect to animal welfare, the conduct of an extended one-generation reproductive toxicity study would be for the present scientifically unjustified."*

You proposed to await the results of OECD TG 422 and OECD TG 414 studies before concluding on the need for an EOGRTS. The OECD TG 414 study does not investigate testicular effects. Therefore, ECHA is of the opinion that the testicular atrophy findings which are observed in existing rat studies warrants further investigation already now.

In the technical dossier you have provided a study record for a sub-chronic toxicity (mice, oral application, 2016) according to OECD guideline 408. ECHA is of the opinion that this mice study is not the most relevant study to address testis toxicity because the rat is known to be a more sensitive species than the mouse towards boron-mediated toxicity leading to testicular atrophy as demonstrated in the international assessments such as ECHA Annex

XV dossier[3] for boric acid and EPA Toxicological review of boron and compounds[4]. Those assessments reported that testicular atrophy was noted in rats in a 90-day study at dose level of 88 mg boron/kg bw/d and at lower incidence also at 26 mg boron/kg bw/d. These dose levels correspond to around 850 and 251 mg/kg bw/d of boron orthophosphate, respectively.

In contrast to that, the testicular atrophy in mice was observed at dose level of 142 mg boron/kg bw/d which corresponds to 1389 mg/kg bw/d of boron orthophosphate and is thus in line with findings of the available sub-chronic toxicity study in mice[5].

In this respect, ECHA emphasises that the REACH Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7.5.4.1) specifies that "*Studies on the most sensitive animal species should be selected as the significant ones, unless toxicokinetic and toxicodynamic data show that this species is less relevant for human risk assessment*".

ECHA considers that testicular atrophy is observed from the rat studies with boric acid and other boron containing compounds in the doses relevant for the risk assessment of the registered substance. Hence, an extended one-generation reproductive toxicity study is an information requirement.

In your comments to the draft decision you disagreed with the information requirement in the draft decision. In addition, you indicated your intention to address the information requirement in an update of the registration.

You outlined in your comments how the information requirement could be addressed by stating that "*We would therefore propose the following tiered approach:*

1. Conduct studies on the dissociation of the compound in different pH-values in order to assess, if boric acid will be formed in concentrations that may be relevant for reprotoxic effects in organisms. A study on resorption or the qualitative assessment of Toxicokinetics could be useful as well. Depending on the outcome, either step #2 or #3 can be implemented.

2. Develop a joint and intelligent OECD 443 testing strategy together with other salts of boric acid, which are currently subject to the EOGRTS. This would be in line with the grouping efforts of Borates and the analogy principles under REACH, endorses REACH Article 13 and moreover would reduce animal testing. Additionally, it would not be so burdensome for individual registrants for conducting very expensive studies individually.

3. Classify and label Boron Orthophosphate pursuant to Annex XI, 1.5 (Column 2 adaptation) according to Boric Acid and in line with the grouping and analogy principle."

ECHA notes that your proposed testing strategy has a number of uncertainties, in particular, whether (1) the results of the hydrolysis study would allow concluding on the relevance of

[3] Annex XV dossier for the identification as SVHC, boric acid, 2010
https://echa.europa.eu/documents/10162/13640/svhc_axvrep_germany_cmr_boric_acid_en.pdf
[4] Toxicological review of boron and compounds, 2004
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0410tr.pdf
[5] ECHA notes that though the sub-chronic toxicity study in mice is not conducted in the most sensitive species regarding testicular atrophy, the information on the sensitive species is available from other sources[3, 4]. ECHA does not consider it necessary to request the sub-chronic toxicity study in rats.

formation of boric acid, (2) an OECD TG 443 testing strategy could be derived based on other salts of boric acid (i.e. read-across approach), (3) such read-across would be acceptable under Section 1.5., Annex XI. In this respect, it is emphasised that ECHA has to make decisions on the currently available data and cannot base them on future results, especially given the identified uncertainties. ECHA however notes that any information provided in a dossier update after the date when the draft decision was notified to you under Article 50(1) of REACH, will be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

A proposal for amendment from a member state competent authority refers to an additional study which is not included in the registration dossier of the registered substance showing that boric acid caused testicular effects already in a 28-day study at 60 mg boron/kg bw/day (Treinen and Chapin, 1991; see registration dossier of boric acid at the ECHA website). This information supports the above discussion of the species sensitivity for the testicular effects of boric acid and also indicates that testicular effects of boric acid may be observed.

In any case, if the results from your proposed OECD TG 422 study show no testicular effects, this would not reduce the concern for testicular toxicity indicated by the results from studies with boric acid. This is because it is very likely that the presence of boric acid as impurity (up to [redacted]%) and the rate of hydrolysis of the registered substance to yield additional boric acid has an impact on the latency period for testicular effects, and therefore longer exposure durations are necessary to clarify the hazard profile of the registered substance with respect to reproductive toxicity.

In your response to the MSCAs proposal for amendments you indicate that you have self-classified the registered substance as Repr. 1B, H360FD (c≥[redacted]%) in a dossier update (submitted on the 23 October 2017 with submission number [redacted]). In your comments you state that the appropriate risk management measures have been introduced. As a consequence, you consider that the request for the extended one-generation reproductive toxicity study is obsolete.

ECHA however notes that while in the updated technical dossier you have classified the substance as Repr. 1B, H360FD, in the updated Chemical Safety Report you indicate that the classification applies only with a specific concentration limit of ≥[redacted]% for boric acid (see pages 32 and 63 of the updated Chemical Safety Report of the registered substance). However, the registered substance boron orthophosphate is defined as containing <[redacted]% boric acid (see section 1.2 of the IUCLID dossier). Therefore, ECHA concludes that the self-classification provided in your updated technical dossier and Chemical Safety Report does not relate to the registered substance and in itself is inconsistent. Therefore, your adaptation according to column 2 of Section 8.7.3. of Annex X based on classification is not valid. Hence, the request for the extended one-generation reproductive toxicity study remains in the decision.

Taken together, ECHA concludes that the EOGRTS is an information requirement according to column 1 of Section 8.7.3., Annex IX.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an

extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

a) The specifications for the required study

Premating exposure duration and dose-level setting

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 the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the 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* R.7a, chapter R.7.6 (version 4.1, October 2015). 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.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 existing 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 IX 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.

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 and consumers as fertilisers in open systems.

Furthermore, there are indications for endocrine-disrupting modes of action because boric acid/ borate shows testicular atrophy in rat studies as explained above.

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 the substance shows endocrine-disrupting mode of action, in particular testicular atrophy.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

b) Outcome

Based on the available information, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./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 some 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;

Notes for your consideration

ECHA notes that the above assessment is based on the information in the registration dossier. With reference to your comments on the draft decision and the observations from a Member State Competent Authority in a proposal for amendment concerning the potential classification, should the registered substance induce relevant testicular toxicity meeting the classification criteria to Repr 1B for fertility in the potentially ongoing OECD TG 422 study, you may consider self-classification and adapt the information requirement, as set out in Column 2 of Section 8.7 of Annex IX.
No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*

R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 27 October 2016.

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.

ECHA received proposal(s) for amendment and modified 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-57 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.