Helsinki, 19 December 2017

Substance name: Benzotriazole
EC number: 202-394-1
CAS number: 95-14-7
Date of Latest submission(s) considered[1]: 22 March 2017
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of Benzotriazole (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on the registered substance Benzotriazole (CAS 95-14-7) as well as some data – as indicated below - for the metabolites of the registered substance 5-hydroxy-1H-benzotriazole (CAS 54013-40-0) and 4-hydroxy-1H-benzotriazole (CAS 26725-51-9):

> *In vivo* test: Fish sexual development test; test method: OECD TG 234 using the registered substance Benzotriazole including a measurement of the registered substance as well as a full analytical metabolite spectrum including at least the metabolites 5-hydroxy-1H-benzotriazole, 4-hydroxy-1H-benzotriazole in test medium and organisms, as further specified in Appendix 1.

You have to provide an update of the registration dossier(s) containing the requested information, including robust study summaries, the complete study reports and, where relevant, an update of the Chemical Safety Report by **26 September 2019**. The deadline takes into account the time that you may need to agree which of the registrant(s) will perform the required tests.

The reasons of this decision and any further test specifications are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This Appendix is confidential and not included in the public version of this decision.

1. Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

2. 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[3] by Leena Ylä-Mononen, Director of Evaluation

[3] 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

Based on the evaluation of all relevant information submitted on Benzotriazole and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for endocrine disrupting properties and evaluate whether an update of exposure and risk estimation is necessary.

Overall concern and information available with respect to endocrine properties

The overall concern evaluated in the substance evaluation was that Benzotriazole has endocrine properties with respect to the environment.

There are two *in vivo* studies available indicating a possible estrogen mode of action of Benzotriazole in two different fish species (i.e. rare minnow *Gobiocypris rarus* and marine medaka *Oryzias melastigma*). In a study with rare minnow *Gobiocypris rarus* by Liang et al. (2014), vitellogenin (VTG) mRNA induction in males and females were seen (significantly increased at 50 µg/L and higher concentrations), which indicates a potential estrogen activity. Also, toxicity against liver cells was observed. From the study by Liang et al. (2014), additionally effects on plasma E2 (estradiol) were seen: In females, plasma E2 was significantly decreased at 5000 µg/L (no dose-response relationship because the increased level at 500 µg/L was not significant). In males, the E2 level was significantly increased at 5000 µg/L (with a clear dose-response relationship). Liang et al. (2014) supposed that there might be different modes of action in females and males based on the different results. Furthermore, the authors wrote that "… in male rare minnows, an increase of expression levels for LHß with a decrease of FSHR [follicle stimulating hormone receptor] and LHR [luteinizing hormone receptor] was observed in this study. This might play some roles in the promotion of E2 and the stimulation of spermatogenesis." It is therefore assumed that effects on steroidogenesis may occur, which are independent from the HPG axis (hypothalamic-pituitary-gonadal axis). Estrogen related effects were also observed in marine medaka (*Oryzias melastigma)* by Tangtian et al. (2012). In this study, VTG gene expression was induced at test concentrations of 10, 100 and 1000 µg/L in males and females. However, only one replicate was used and statistics were therefore insufficient.

Two further studies with two other fish species also evaluated endocrine effects of Benzotriazole, but could not demonstrate clear effects. Harris et al. (2007) tried to examine anti-estrogen effects in adult fathead minnows (*Pimephales promelas*) at concentrations of 10, 100, and 1000 µg/L. Male fish were co-exposed to Benzotriazole and E2, whereas females were exposed only to Benzotriazole. Plasma vitellogenin concentrations and gonadosomatic indices could not show any significant anti-estrogenic activity in males nor females, which was previously demonstrated in *in vitro* assays. Fent et al. (2014) could not show any clear endocrine related significant effects on eleuthero embryos of the zebra fish *Danio rerio* (2-4 hpf) after exposure for 6 days to 10, 100, and

1000 µg/L (nominal; 8, 97, 1197 µg/L measured) Benzotriazole. Benzotriazole led to a slightly but not significant up-regulated VTG mRNA gene expression at 1197 µg/L (measured). In parallel *in vitro* assays (YES, YAS), Benzotriazole had no estrogenic nor androgenic effects, but showed significant anti-androgenic activity.

For other species there is only limited data. A study (Kadar et al. 2010) with an invertebrate, i.e. the protochordate *Ciona intestinalis*, showed malformations and a delayed settling in concentrations of 32 and 100 µg/L which could be endocrine-mediated.

Hence, there are indications for estrogenic effects *in vivo* for (male) fish (e.g. VTG mRNA elevation *in vivo*), that make an estrogenic mode of action plausible. However, the *in vitro* tests available for Benzotriazole do not indicate estrogenic properties, but rather anti-estrogen or anti-androgen effects.

Moreover, the effects of Benzotriazole observed in the two *in vivo* studies could be caused by metabolic transformation products which were formed in the test organisms. Unfortunately, *in vitro* studies that included a metabolic activation or assessed the known metabolites of Benzotriazole were not available. Possible metabolic transformation products of Benzotriazole were described by Stouten et al. (Stouten, 2000) who exposed a microsome suspension of rat livers to Benzotriazole and found 5-hydroxy-1H-benzotriazole and 4-hydroxy-1H-benzotriazole (1.6 vs. 0.32 % of the amount). The functional OH group of 5-hydroxy-1H-benzotriazole and 4-hydroxy-1H-benzotriazole is a structural alert for a potential estrogenic activity. Hence, endocrine *in vivo* effects might indeed be caused by the metabolites 5-hydroxy-1H-benzotriazole and 4-hydroxy-1H-benzotriazole which also may be formed in fish, or even further metabolites formed by degradation.

In addition to being formed during metabolisation in the organism, the metabolites may also be formed outside the fish (Leitner and Roshani 2010). According to Leitner and Roshani (2010), a hydroxylation of Benzotriazole is possible in the environment. Moreover, the hydroxyl-metabolites are known to be excreted via human urine (measurements of general populations in 7 countries) and thus might enter municipal sewage (Asimakopoulos et al. 2013). Also further metabolites may be formed via degradation in the environment, such as e.g. di-hydroxy-1H-benzotriazole, possess the structural alert of the functional OH group for a potential estrogenic activity. Huntscha et al. (Huntscha et al. 2014) analysed several Benzotriazole transformation products in wastewater effluents, showing their environmental relevance. It should be noted that, although Benzotriazole has been frequently found in the environment (Loos et al. 2009, 2010, among others), the hydroxy-metabolites were not in the focus of monitoring studies. Hence, only few information on their environmental occurrence is available. If the hazards/risks of Benzotriazole are addressed, also the metabolites would be covered.

Reasoning for the requested test

In vivo testing of Benzotriazole with a Fish Sexual Development Test including chemical measurements of the parent substance and the above mentioned metabolites are warranted.

The information from available in vivo studies indicate a possible estrogenic mode of action (MoA) in fish (e.g. VTG mRNA elevation). However, together with the available in vitro studies, there are indications that further modes of action are possible and also metabolites may cause the effects in vivo. The Fish Sexual Development Test (FSDT, OECD TG 234) is an adequate long-term test in this case in light of the available indications for an estrogenic mode of action and also gives indications for further underlying modes of action. The FSDT assesses early life stage effects and potential adverse consequences of putative endocrine disrupting chemicals (e.g. estrogens, androgens and steroidogenesis inhibitors). This test is required to provide a biologically plausible link between endocrine (adverse) effects in vivo and the underlying mode of action which would be necessary for an SVHC (substance of very high concern) identification and possible further risk management measures.

As there are indications that different modes of action (e.g. estrogen, androgen) may be possible, as much information as possible should be gained from the *in vivo* test. Therefore the FSDT should cover all endpoints described in the technical guideline as well as histopathological investigations (see also note for consideration with respect to additional recommendations).

The FSDT shall be conducted using Benzotriazole as a test substance. As there are indications that formed metabolites might be responsible for the endocrine effects, the measurement of Benzotriazole and an analytical metabolite spectrum including the two main metabolites in test medium and test organisms are to be included as specified below. This will help to gain understanding on the excreted metabolites or further metabolites that are produced via degradation in the test medium.

An additional direct testing of metabolites in the FSDT is currently not needed. As chemical analyses are anyway mandatory to monitor stability of test substances during the test to confirm the applied concentrations, it should be appropriate and cost-efficient to measure the metabolites in the test medium in parallel.

From the currently available information from existing in vivo studies, it is expected that the FSDT will show endocrine effects triggered by an estrogenic mode of action (MoA) though other MoAs may not be excluded. Depending on the results obtained in the now requested FSDT test and any other relevant information, the need for further tests will be considered in the follow-up.

The necessity to clarify potential risks with more information

The new information is necessary to decide on whether or not the substance should be considered as a substance of very high concern (SVHC) based on its potential endocrine

disrupting effects, and/or that of its metabolites, with respect to the environment. If so, further risk management measures might be needed.

The substance is not biodegradable in fresh water and the marine environment. Furthermore, Benzotriazole is produced in a tonnage of more than 1000 t/a, and has a wide dispersive indoor and outdoor use. The available monitoring data indicate that Benzotriazole is frequently found in environmental compartments, i.e. it is regularly measured and detected in surface waters, sewage treatment plants, as well as ground waters across Europe (Loos et al. 2009 & 2010).

Fish sexual development test; test method: OECD TG 234 using the registered substance Benzotriazole including a measurement of the registered substance as well as a full analytical metabolite spectrum including at least the metabolites 5-hydroxy-1H-benzotriazole, 4-hydroxy-1H-benzotriazole in test medium and organisms

The concern(s) identified

As described in the section above, there are indications that Benzotriazole has endocrine disrupting properties, as indicated by *in vitro* tests and observed in *in vivo* tests. However, results are contradictory and the underlying mode of action, as well as resulting adverse effects *in vivo* are not clarified yet.

Why new information is needed

The requested *in vivo* test, a Fish sexual development test; test method: OECD TG 234 is needed to conclude on the endocrine-mediated effects on fish *in vivo* and to clarify the underlying mode of action.

Based on data from a Fish sexual development test; test method: OECD TG 234 a conclusion might be drawn on whether or not Benzotriazole is an endocrine disrupter or is metabolised to an endocrine disrupter in fish with an (anti-)estrogenic, (anti-)androgenic mode of action or via an inhibition of steroidogenesis. If identified as an endocrine disruptor the substance may become a candidate for identification as substance of very high concern or other regulatory activities that will be determined afterwards.

The requested test is a level 4 study of the Conceptional Framework (OECD, 2012). At this level *in vivo* studies provide data about endocrine modes of action and related adverse effects.

In the follow-up to substance evaluation, the evaluating MSCA will consider on the basis of all available and relevant information including the results of the now requested test whether further information will be necessary.

Considerations on the test method and testing strategy

A Fish sexual development test (OECD TG 234) shall be performed.

The test should consider all relevant endpoints to obtain as much information as possible.

The most relevant environmental exposure route is water. The test shall be conducted under flow-through conditions. The high water solubility of Benzotriazole (19.8 g/L) allows water borne exposure.

Study design, specific instructions and modifications from standard approach

All endpoints listed in the TG 234 need to be addressed (such as hatching rate, survival, length, body weight). In addition to the specifications in the OECD TG 234, the following specific test conditions need to be considered:

Species

The validated test species for the FSDT are zebrafish, stickleback and medaka. Stickleback is not the recommended species for hazard and risk assessment and therefore should not be used. In your comments to the proposals for amendments you expressed preference for using the zebrafish. The choice of test species should be justified in accordance with the test guideline and based on existing studies available in literature (see citations in section on overall concern and information available).

Gonad histopathology

Gonadal histopathology and staging of the gonads shall be examined because they may give additional information that is necessary to conclude on the final result. Gonad histopathology should be performed referring to OECD GD 123 (OECD, 2010; Guidance document on the diagnosis of endocrine-related histopathology in fish gonads).

Liver and kidney histopathology

Histopathological examination of the liver and the kidney should be performed. Potential liver toxicity was suggested by Liang et al. (2014).

VTG measurements

The VTG level shall be determined in plasma according to the OECD 234 guidance.

Sex determination/sex ratio

Sex determination should be based on gonadal histopathology. The genetic sex determination and determination of secondary sex characteristics shall also be included if the determination of the parameters is possible for the selected test species as it increases the statistical power of sex determination and the detection of phenotypic sex reversal (e.g. in case medaka is used).

Use of a specific pH value

The pK_a value of Benzotriazole is about 8 (Katritzky et al. 1991). As the pK_a value is near the normal test conditions, the pH value for the testing with Benzotriazole and the metabolites should be maintained as close as possible to 7.0 to minimize ionization of the test material; flow-through test conditions are to be used. At higher pH values

Benzotriazole and the hydroxybenzotriazole-metabolites would lose the H-protons from the triazole part.

Test concentrations

Only the registered substance Benzotriazole is to be tested.

The experiments are to be designed following the guideline. A medium control and at least 5 test concentrations are to be selected according to the TG 234 depending on the selected test species and available studies (see also references cited above). It should both ensure that observable effects are induced and safeguard the feasibility to identify and quantify the parent substance and its metabolites. As the substance is very well soluble in water, use of a solvent is not necessary.

Chemical analysis

Chemical analyses shall be performed both for the registered substance Benzotriazole, as well as an analytical metabolite spectrum covering the metabolites 5-OH-1H-benzotriazole (5-hydroxy-1H-benzotriazole), CAS 54013-40-0, 4-OH-1H-benzotriazole (4-hydroxy-1H-benzotriazole), CAS 26725-51-9, and preferably further metabolites like e.g. di-hydroxy-1H-benzotriazole. This will help with interpretation of the study results and to distinguish whether any observed effects are caused by the parent substance or its metabolites (see section above). It is helpful if further metabolites – if such occur during analysis of the metabolite spectrum – are identified and quantified if technically feasible.

The measurements should be performed both in test media and in fish: Chemical analyses for substance and metabolites in test media should be performed at the beginning and the end of the test for all treatments and replicates to obtain statistically valid results and additionally weekly for one replicate as described in the test guideline 234. The respective concentrations in the test organism should be measured at the end of the test for all treatments, at least for the treatments where significant effects in any of the investigated endpoints were observed and the controls. Measurements of concentrations in the fish shall be done as technically feasible (for example whole fish or tail/head homogenates). As pointed out in your comments to the proposals for amendments, additional test chambers and fish may be used to accommodate the measurement of metabolites alongside those fish required for both the histopathological investigations (liver, kidney, gonads) and the VTG measurements (in plasma, see above). It is necessary for pooled analyses to separate males from females and the treatment replicates need to be maintained while pooling organisms.

<u>Study Report</u>

You shall submit the full study report for the information required. A complete rationale and access to all available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed to fully assess the provided information and to efficiently clarify the concerns.

Consideration of alternative approaches

The request for a Fish Sexual Development Test (TG 234) is suitable and appropriate to obtain information that will allow clarifying whether the endocrine properties of Benzotriazole pose a concern for the environment.

More explicitly, there is no equally suitable alternative available, since the study provides information on indicative adverse effects. The FSDT (TG 234) is a level 4 study of the OECD Conceptual Framework (OECD 2012) which provides information on endocrine effects in a more thorough assessment than level 3 studies like OECD 229. The FELS test (OECD test guideline 210) would not reveal endocrine mediated effects. The OECD TG 229 (fish short term reproduction assay) covers the reproductive phase, but is only a screening test on CF level 3 with less statistical power – a negative result obtained here would not be sufficiently conclusive to "overwrite" the already available *in vivo* test results. Although such test would be sufficient to decide on a substance with a clear estrogenic or (anti-)androgenic mode of action, in this case, due to the assumption that different mode of actions might be involved, a lack of adverse effects and/or indications for a MoA might be due to differences in sensitivity of life stages. The much more expensive alternative would be a fish full life-cycle test (FFLC), but this involves a disproportionate effort. If the data, once obtained, confirm that the substance is an endocrine disruptor for the environment, it will allow authorities to consider further regulatory risk management, e.g. SVHC identification.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the substance subject to this decision:

Fish sexual development test; test method: OECD 234 using the registered substance Benzotriazole including a measurement of the registered substance as well as a full analytical metabolite spectrum including at least the metabolites 5-hydroxy-1H-benzotriazole, 4-hydroxy-1H-benzotriazole in test medium and organisms.

Consideration of your comments on the draft decision and proposals for amendment

One Member State proposed to include liver and kidney histopathology which you agreed to in your comments and which was added to the information requirement, respectively. The original test strategy required VTG determination from liver homogenate. As the liver shall now be used for histopathological examination, to avoid the need to include additional animals, VTG shall be determined from plasma instead as described above.

Note for consideration: Recommended additional measurements in the in vivo test

The original testing strategy included further *in vitro* testing to be performed alongside the *in vivo* test to clarify the underlying mode(s) of action. Based on proposals for amendment made during the decision making process, immediate *in vitro* testing was removed from the information requirements. You may consider additionally to include measuring hormonal levels in the plasma samples used for the mandatory determination

of VTG. Such further measurements may include hormones whose alteration may be indicative of a MoA according to the EATS (estrogen, androgen, thyroid and steroidogenesis) pathways, i.e. determination of β-estradiol for an (anti-)estrogenic or steroidogenesis MoA (see Liang et al., 2014, e.g. elevated E2 levels). The determination of thyroid hormones may indicate a potential thyroidal mode of action. Such additional measurements may be conducted using the plasma samples obtained for VTG level determination. Quantitative analysis might for example be achieved by using the respective Enzyme-linked Immunosorbent Assays (ELISA).

In the comments to the draft decision sent to you initially you indicated agreement to the required OECD TG 234. However, you expressed concern that the studies might not be completed in time due to limited availability of testing laboratories taking into account the initially proposed deadline. ECHA took this comment into account and set the deadline for the required *in vivo* test to 21 months.

In your comments to the proposals for amendments from three Member States you agreed on conducting gonad histology, as well as histopathology of liver and kidney according to OECD GD 123 and noted that additional test chambers and fish will be needed to cover histopathology, VTG and chemical measurements. You further agreed on using at least one higher test concentration to be able to identify and quantify the parent substance and metabolites in fish/water. You noted that no bioaccumulation is expected and the use of full fish homogenates are expected necessary to monitor concentrations in fish, and that concentrations in water are expected to be below or close to the LOD due to the flow-through test design. These comments are in line with the adapted draft decision following the proposals for amendments.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and based on initial grounds for concern relating to its potential properties as an endocrine disruptor to and exposure of the environment, Benzotriazole, CAS No 95-14-7 (EC No 202-394-1), was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The Competent Authority of Germany (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the concern of endocrine disruption to the environment. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 9 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation as described below.

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

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account the late comments from you and they are reflected in the Reasons (Appendix 1). The requested information was not changed in response to the submitted comments. However, the deadline for providing the information was adapted.

Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposals for amendment to the draft decision and modified the draft decision. The *in vitro* tests (steroidogenesis assay OECD TG 456 and E-screen assay) were removed. The proposals for amendment are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendments.

Your comments on the proposed amendments were taken into account by the Member State Committee.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-56 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

EUROPEAN CHEMICALS AGENCY

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

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 relation to the required experimental study/ies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.