ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114367119-44-01/F
Substance name: Tributyl O-acetylcitrate
EC number: 201-067-0
CAS number: 77-90-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 24.10.2013
Registered tonnage band: 1000+T

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. **Spectral data (Annex VI, Section 2.3.5);**
   - **Nuclear magnetic resonance or mass spectrum**

2. **Description of the analytical methods (Annex VI, Section 2.3.7);**

3. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471);**

4. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) provided that the study requested under 3. has negative results;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

6. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

7. *** Available two generation reproductive toxicity study to fulfil the information requirement for an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3., column 2; test method: EU B.35./OECD TG 416) in rats, oral route with the registered substance.**

In accordance with Articles 27 and 30 of the REACH Regulation you are required to obtain the information indicated in point 7 of the present decision from the registrant referred to in

* This information has been submitted by a registrant in an individual registration of the same substance, as available on ECHAs dissemination website (see cover letter to this decision).

the cover letter of this decision.

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.

You are required to submit the requested information in an updated registration dossier by **31 January 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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[2] by Kevin Pollard, Head of Unit, Evaluation E1

[2] 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

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.

1. Spectral data (Annex VI, Section 2.3.5.)

"Spectral data" is an information requirement as laid down in Annex VI, Section 2.3.5. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

Your registration dossier does not contain the full set of analytical data for the registered substance. You have provided only an infra-red (IR) spectrum, which alone is not sufficient to identify the substance. No ultra violet (UV) spectrum and nuclear magnetic resonance (NMR) spectrum (or a mass spectrometry (MS) spectrum as an alternative to an NMR spectrum), as required by Annex VI Section 2.3.5 of the REACH Regulation, have been included in your registration dossier. The following justifications for not providing the UV and NMR spectra were given: "*This test technique has not been applied, because it will not provide additional information. Detailed compositional analysis can be obtained by HPLC; further qualitative evidence can be obtained by utilising FTIR since an IR spectrum can provide both generic information, about the types of functional group within the compound and, by matching against a reference material or spectrum, provide a proof of identity. Finally, although NMR spectroscopy would be technically feasible, it does not appear scientifically necessary - the test methodologies applied will be entirely sufficient for an unambiguous substance identification.*" and "[...] *Finally, although UV/Vis spectroscopy would be technically feasible, it does not appear scientifically necessary - the test methodologies applied will be entirely sufficient for an unambiguous substance identification.*"

ECHA regards this required information necessary for the identification of the registered substance and considers the justification provided not scientifically acceptable. In fact, the IR spectrum displays characteristic vibration bands for the covalent bonds of organic compounds such as the registered substance, however information such as the length and nature of the aliphatic chain cannot be provided by IR alone. NMR spectroscopic analyses such as a ^{1}H-NMR and ^{13}C-NMR are powerful tools for structure characterisation and elucidation due to characteristic chemical shifts and spin-spin couplings, which also reflect the relative abundance of individual atoms.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to include in your registration dossier an NMR (or MS) spectrum of your substance. You shall ensure that the operating parameters used for recording the spectrum are specified in the dossier.

As for the reporting of the spectral data in the registration dossier, the information should be included in IUCLID section 1.4.

Further technical details on how to report the spectral data in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

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

Annex VI, Section 2.3.7. of the REACH Regulation requires that each registration dossier contains a sufficiently detailed description of the analytical method used for establishing the composition of the registered substance and therefore its identity. This information shall be sufficient to allow the method to be reproduced.

You have provided in IUCLID section 1.4 a copy of a gas chromatogram, as well as a peak table with associated retention time and peak areas. However ECHA notes that the description of the method used to generate this gas chromatogram was not provided.

Without a detailed description of the method used to establish the composition of the registered substance it is not possible to reproduce it as required by Annex VI, 2.3.7. of the REACH Regulation.

In line with Annex VI Section 2.3.7. you are requested to submit a suitable description of the analytical methods (chromatography or any other suitable analytical method) used for the quantification of the registered substance.

The description shall be sufficient for the methods to be reproduced. For chromatographic methods, the following minimum information needs to be reported; details on sample/standard preparation, column specification, and identification of carrier gas/eluent and type of detector.

You shall ensure that the analytical information is supporting the composition in section 1.2 of the IUCLID dossier.

As for the reporting of the above data in the registration dossier, the information should be attached in IUCLID section 1.4.

Further technical details on how to report the description of the analytical methods in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

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

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

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided two study records for Bacterial Reverse Mutation Assays (OECD TG 471; Ames test). ECHA has evaluated these studies according to Annex XI, Section 1.1.2. According to that provision data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

1. The first study, [redacted] (1982), was not performed according to GLP. This study does not provide the information required by Annex VIII, Section 8.4.1., because key parameters foreseen to be investigated in the test method OECD TG 471 were not covered. More specifically, the substance was tested up to 495 µg/plate without justification why the limit dose of 5000 µg/plate was not tested. Also, the study was conducted only without, but not with, metabolic activation (S9 mix), and does not include a fifth test strain as explained further below. In addition, the study documentation is insufficiently describing details of the study (induction ratio, dose-effect, reproducibility, choice of doses, protocol details (pre-incubation)). Therefore, ECHA cannot judge on the adequacy of its reliability. Hence, according to Annex XI, Section 1.1.2., ECHA concludes that the study design and documentation are inadequate to fulfil the information requirement.

2. The second study, [redacted] (1991), was performed according to GLP. This study does not provide the information required by Annex VIII, Section 8.4.1., because key parameters foreseen to be investigated in the test method OECD TG 471 were not covered. More specifically, test concentrations were not described, and the test does not include a fifth test strain, as explained further below. In addition, the study documentation is insufficiently describing details of the study (induction ratio, dose-effect, reproducibility, choice of doses, protocol details (pre-incubation)). Therefore, ECHA cannot judge on the adequacy of its reliability. Hence, according to Annex XI, Section 1.1.2., ECHA concludes that the study design and documentation are inadequate to fulfil the information requirement.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

As indicated above, one key parameter missing in the two studies you provided in the technical dossier, which used different strains of *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100, is the inclusion of strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) into the test. Since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided studies do not meet the current guidelines, nor can they be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA

(pKM101), or *S. typhimurium* TA102 has not been submitted and that a test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments to the draft decision submitted according to Article 50(1) of the REACH Regulation, you refer to an available carcinogenicity study and you explain that "*The ability of substances to induce mutations or genotoxicity (as defined in Section R.7.7.1) can be indicative of carcinogenic potential. However, correlations between mutagenicity/ genotoxicity and carcinogenesis are stronger when effects are observed in appropriately designed in vivo as opposed to in vitro studies. [...] According Figure R.7.7.2 Integrated Testing Strategy for carcinogenicity the classical 2-year carcinogenicity test information is sufficient to decide on both C&L and risk characterization. For the substance of concern this classical data for carcinogenicity are available with the advantage to identify non-genotoxic carcinogens, as well. According to Annex XI, section 1.1 Testing does not appear scientifically necessary because of use of existing data. This study fulfils the requirements of Annex XI, Section 1.1.2. The RMOA evaluation (ANSES 2016) comes to the following conclusion [...] ATBC did not produce neoplastic lesions in any of the dose groups up to the highest dose (1000 mg/kg bw/d) tested and has therefore no carcinogenic potential in rats.]*"

ECHA observes that the existing carcinogenicity study is indicative of an absence of genotoxic modes of action with respect to carcinogenic potential of the registered substance and the RMOA conclusion relates to the carcinogenic potential of the registered substance. However, the classification for mutagenicity also concerns germ cell mutagenicity, which cannot be adequately assessed by the provided information. Therefore, ECHA concludes that a carcinogenicity study in itself is insufficient to conclude on the mutagenic potential of a substance. The concern for gene-mutations is supported by DNA-binding alerts in the OECD QSAR toolbox profile of the registered substance.

Please take note of the "notes for your consideration", below.

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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, 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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

Notes for your consideration

ECHA notes that this test is already available in the registration dossier of another registrant for the same substance. In the alternative to conducting the above test, you may request it from that registrant pursuant to the process set out in Article 30 of the REACH Regulation. You can find further information on the Article 30 process in the ECHA *Guidance on data sharing* (version 2.0, April 2012). Therefore, you should seek to fulfil the above information request for this study by providing a robust study summary within the meaning of Article

3(28) of the REACH Regulation. It is stressed that it is your responsibility to assess the quality and and relevance of the information and to submit a robust study summary meeting the criteria of Article 3(28).

4. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that negative results were obtained in an *in vivo* micronucleus test and in the two bacterial gene mutation studies which ECHA considers as having shortcoming and being reported inappropriately. Therefore, adequate information on *in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under 3. has negative results.

In the technical dossier you have provided a study record for an *In Vitro* Mammalian Cell Gene Mutation Test (OECD TG 476; [redacted] 1991) marked as reliability 2 by you. However, this study does not provide the information required by Annex VIII, Section 8.4.3., because of inadequate documentation. More specifically, the study documentation is insufficiently describing details of the study (e.g., test concentrations used, reproducibility, negative controls, statistics, and cytotoxicity). Therefore, ECHA cannot judge on the adequacy of its reliability. Hence, ECHA considers that the study design and documentation are inadequate to fulfil the information requirement.

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.
ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision submitted according to Article 50(1) of the REACH Regulation, you "*refer to the comments on endpoint: In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)*". ECHA therefore refers to the explanation under request 3), above, and the notes for consideration under this request, below.

Therefore, 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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490), provided that the study requested under 3. has negative results.

Notes for your consideration

ECHA notes that this test is already available in the registration dossier of another registrant for the same substance. In the alternative to conducting the above test, you may request it from that registrant pursuant to the process set out in Article 30 of the REACH Regulation. You can find further information on the Article 30 process in the ECHA *Guidance on data sharing* (version 2.0, April 2012). Therefore, you should seek to fulfil the above information request for this study by providing a robust study summary within the meaning of Article 3(28) of the REACH Regulation. It is stressed that it is your responsibility to assess the quality and and relevance of the information and to submit a robust study summary meeting the criteria of Article 3(28).

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a 12-month toxicity study with pairing of animals in the 9th month and subsequent examination of reproductive parameters and offspring ([redacted] 1977) in both rats and mice (rodent species), by the oral route with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.7.2.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.1.2. However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 1.1.2 quoted in section 3 of this decision.

More specifically, the study does not adequately and reliable cover the key parameters foreseen to be investigated in a pre-natal developmental toxicity study according to OECD TG 414. A study according to OECD TG 414 requires – *inter alia* - caesarean section and skeletal and visceral staining of the foetuses. However, in the provided study, post-natal effects on the offspring after natural delivery were investigated. Hence, the study is also not adequate for the purpose of classification and labelling and/or risk assessment. In addition, no adequate and reliable documentation of the study was provided.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation, you provided further information. Following ECHA Guidance R.7.a Section 7.6.2.3.2 you referred to the adaptation possibilities of Annex XI, Sections 1.1.2. (existing information not carried out according to test methods), 1.2. (weight of evidence), 1.3. (QSAR), and 1.4. (*in vitro* methods). You provided summaries on the following available information:

1) Non-guideline 12-month toxicity study with pairing of animals in the 9th month and subsequent examination of reproductive parameters and offspring in both rats and

mice ([redacted] 1977);
2) Two-generation study (OECD 416, [redacted] 1994);
3) Sub-chronic toxicity study with an *in utero* exposure phase (*Chase & Willowby* 2002, cited in US EPA 2003);
4) Danish (Q)SAR prediction not indicating a teratogenic potential for ATBC in humans;
5) Combined chronic toxicity/carcinogenic study ([redacted] 2005).

You further explain that "*Within this lifecycle assessment for adverse health effects no reproductive/developmental toxicity findings were observed. The major manifestations of developmental toxicity that may serve as trigger for further studies are death of the organism, structural abnormalities, altered growth, and functional deficiencies.*"

ECHA already provided an explanation further above why the study 1) referred to in your comments is inadequate to fulfil the information requirement. The same explanation is applicable to studies 2), 3), and 5). In addition, the (Q)SAR prediction 4), while useful to complement existing data, in this case is insufficient on its own to provide reliable information on pre-natal developmental toxicity (including growth, survival, external, skeletal and visceral alterations).

ECHA notes that an adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/ conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a pre-natal developmental toxicity study (EU B.31/OECD TG 414). Relevant elements are in particular investigations to detect pre-natal developmental toxicity including growth, survival, external, skeletal and visceral alterations.
ECHA observes that the information you provided does not adequately address the relevant elements of a pre-natal developmental toxicity study because you did not provide sufficient information on skeletal and visceral alterations. Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, Section 8.7.2.

Therefore, ECHA concludes that the provided information is insufficient to meet the information requirements for this endpoint. Therefore, your adaptation of the information requirement is rejected.

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.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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 liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, 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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Notes for your consideration

ECHA informs you that the registrant of the individual submission for this substance has received the same request for a pre-natal developmental toxicity study in a first species (hereafter referred to as the "individual registrant"). ECHA expects you and the individual registrant to coordinate and agree who shall perform the test on behalf of all registrants for the same substance, according to REACH Article 53, to avoid unnecessary testing on vertebrates.

6. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

In the technical dossier you have provided a study record for a 12-month toxicity study with pairing of animals in the 9th month and subsequent examination of reproductive parameters and offspring ([redacted] 1977) in both rats and mice (rodent species), by the oral route with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.7.2. as explained above under section 5.

In the comments according to article 50(1) of the REACH Regulation, you "*refer to the comments on endpoint: Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species*". ECHA therefore refers to the explanation under request 5), above, and the notes for consideration under this request, below.

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.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, 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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

ECHA informs you that the individual registrant of the joint submission for this substance has received the same request for a pre-natal developmental toxicity study in a second species. ECHA expects you and the individual registrant to coordinate and agree who shall perform the test on behalf of all registrants for the same substance, according to REACH Article 53, to avoid unnecessary testing on vertebrates.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X 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 X. 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 the 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

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement. You provided the following justification for the adaptation: *"The toxicokinetics of ATBC were investigated in rats with oral exposure (see section 7.1.1) and the results are not indicating a bioaccumulation potential. Longer-term studies with oral dosing gave no indication for adverse effects on reproductive organs. Therefore, adverse effects concerning toxicity to reproduction are not to be expected and there is no scientific justification for planning further animal tests to investigate this endpoint."*

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence.

You have provided the following sources of information under "repeated dose toxicity", to which you refer in your justification:

- Sub-chronic toxicity study (90-days) in rats, oral route (feed), (OECD TG 408; GLP) with the registered substance, [redacted] 2005 (study report), rel. 1, NOAEL 1000 mg/kg bw/d (transient changes in liver, slight changes in clinical chemistry).

- Combined chronic repeated dose toxicity/carcinogenicity study in rats, oral route (feed) (OECD TG 453, GLP) with the registered substance, [redacted] 2005 (study report), rel. 1, NOAEL 300-1000 mg/kg bw/d (slight increase in liver weights and on centrilobular hypertrophy in the liver noted at 1000 mg/kg bw/day in both sexes).

ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and assessed whether you have provided "sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property" with respect to the information requirement of Annex X, Section 8.7.3. for the registered substance (see 'specification of the study design').

ECHA has further evaluated the information according to ECHA Guidance R.4.4. by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated whether the provided information is consistent and covers the relevant aspects of information on "sexual function and fertility" of the parental generation(s) and on "developmental toxicity" observable peri- and postnatally in the offspring generation(s) as specified at Annex X, Section 8.7.3.

ECHA notes that the adaptation you provided does not explain how the provided information would address the information as required for Annex X, Section 8.7.3.

ECHA notes that with respect to "sexual function and fertility" of the parental generation these studies provide information on the histopathological examination of reproductive organs in male and female animals after sub-chronic and chronic exposure. However, they do not provide information with respect to male and female reproductive performance (such as gonadal function, mating behaviour, conception, development of the conceptus and parturition), sperm parameters, and oestrus cycles,

ECHA further notes that with respect to the aspect of "developmental toxicity" observable peri- and postnatally" in the offspring generation(s), you have provided a "*12-month toxicity study with pairing of animals in the 9th month and subsequent examination of reproductive parameters and offspring*" ([redacted] 1977) in both rats and mice (rodent species) under "developmental toxicity". ECHA observes that you consider this study as reliable with restrictions and you indicate that "*Data are reliable but reference lacks details*".

However, ECHA is of the opinion that a study performed in 1977 (not according to GLP and a test method), and that was published in a journal (Gig Sanit) can be considered only as reliable in case all relevant information is provided. In the absence of all relevant information on the performance of this study (e.g., animal number, strain of rats and source of animals, day of post-natal investigations), and since the highest dose tested (250 mg/kg bw/d) did not lead to any effects, the provided information cannot be considered as appropriate to be used as an element in a weight of evidence adaptation to conclude on the hazard of the registered substance with respect to post-natal effects.

Therefore, ECHA concludes that the evidence you provided to adapt the standard information requirement for an extended one-generation reproductive toxicity study together with your justification is not sufficient according to Annex XI, Section 1.2. to assume/conclude that the substance has not hazardous properties with regard to sexual function and fertility and developmental toxicity. Consequently, your adaptation of the information requirement is rejected.

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.

Pursuant to the second column of Annex X section 8.7.3 Two-generation reproductive toxicity studies (B.35, OECD TG 416) that were initiated before 13 March 2015 shall be considered appropriate to address this standard information requirement.

ECHA notes that this information requirement can be fulfilled with an existing two-generation reproductive toxicity study (OECD 416) performed with the registered substance that was provided by another registrant in a parallel individual registration outside your joint registration.

In accordance with Title III of the REACH Regulation, namely the obligations to request access to available information of studies on vertebrate animals (Articles 27 and 30 of the REACH Regulation), you shall not perform new testing involving vertebrate animals in order to comply with the present decision where such data is already available and are required to request this information from other registrants of the same substance.

More specifically, Article 30(1) of the REACH Regulation requires you to request other substance information exchange forum (SIEF) participants to share the studies involving tests on vertebrate animals already available. You and the individual registrant shall make every effort to ensure that the costs of sharing the information are determined in a fair, transparent and non-discriminatory way.

In addition, you are reminded of the obligation imposed by Article 11 of the REACH Regulation on all the registrants of the same substance to submit registrations for the same substance jointly. ECHA encourages you to ensure that you and the other registrant are part of one single joint submission.

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 5 October 2016.

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 requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally 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.

4. In case the required test(s) is/are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide 6 "How to report on read-across". This is required to demonstrate that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.