EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350319-49-01/F
Substance name: 4-tert-butylpyrocatechol
EC number: 202-653-9
CAS number: 98-29-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30.09.2014
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. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**

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

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 **21 December 2017**. 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.

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Appendix 1: Reasons

1. **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.

In the technical dossier you have provided a study record for a study equivalent or similar to OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test) with the registered substance. However, this study does not provide the information required by Annex VIII, Section 8.4.3., because there are deficiencies in the test provided which do not allow a conclusion to be reached on the potential for gene mutation in mammalian cells.

You argue that the test results are questionable due to very high level of cytotoxicity (Relative Total Growth < or = to 10%) at the concentrations of 4.5 or 5 µg/mL that induced an increase in mutation frequency. Nevertheless, the test was performed only without metabolic activation and therefore the provided information is incomplete. The testing guideline OECD 476 clearly states in the principle of the test method that "*Cells in suspension or monolayer culture are exposed to the test substance, both with and without metabolic activation*".

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.

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).

2. **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).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement stating that "*A prenatal developmental toxicity study in a first species has been performed* [redacted]. *Based on this study conducted in rats after oral exposure, 4-tertbutylpyrocatechol does not induce teratogenic effects. Taken into account all relevant data available on this substance and especially repeated dose toxicity studies, a reproductive toxicity alert, consisting of altered sperm and estrous cycle parameters, was observed. Furthermore, based on the OECD 414 guideline study* [redacted] *no developmental effect is expected* [redacted]."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2 or the general rules for adaptation of Annex XI. It does not fulfil the criteria of Annex X, Section 8.7.2.,column 2 because the substance is not a known genotoxic carcinogen, it is not a known germ cell mutagen, it is toxic and systemically available and it did not cause developmental toxicity in the first study. 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. However, a prenatal develomental study in one species, and alerts for reproductive toxicity from a Repeated Dose 90-Day Oral Toxicity cannot be seen as sufficient evidence "*from several independent sources of informatiopn leading to the assumption that a substance has or has not a partcilar dangeours property while the information from each single source alone is regarded as insufficient to support this notion.*" An available prenatal developmental toxicity study in a first species with negative findings and a repeated dose study cannot alter the legal requirement for a prenatal developmental toxicity study in a second species because a study in a second species may reveal prenatal developmental toxicity that was not shown in the first species.

Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision you state that [redacted]

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.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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 solid, 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) by the oral route.

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 17 August 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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

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

3. 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.

4. 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.

5. ECHA notes that there is an ongoing testing proposal examination for an OECD 416 two-generation reproductive toxicity study which has been referred to the European Commission for assessment in accordance with article 51(7) of the REACH Regulation. Consequently, the information requirement of Annex X section 8.7.3. is not addressed in this compliance check decision.