EUROPEAN CHEMICALS AGENCY

Helsinki, 25 October 2016

Addressee: [redacted]

Decision number: TPE-D-2114346823-46-01/F
Substance name: Esterification products of 4,4'-isopropylidenediphenol, ethoxylated and prop-2-enoic acid.
EC number: 613-584-2
CAS number: 64401-02-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08.06.2016
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

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

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

1. **In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2; test method: OECD TG 474) in mice or rats, oral route using the registered substance, if it can be demonstrated that the substance or its metabolites will reach the bone marrow; or**

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum using the registered substance;

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance;**

3. **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 using 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 **1 November 2018**. 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[1] by Hannu Braunschweiler, Head of Unit, Evaluation E1.

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

1. **In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2)**

   or

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)

Pursuant to Article 40(3) of the REACH Regulation, ECHA may require the Registrant (a) to carry out the proposed test, (b) to carry it out under modified conditions, or (c) to carry out a different test, if the testing proposal is not (fully) compliant with the requirements in the Annexes to the REACH Regulation.

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains:

- A Bacterial Reverse Mutation Assay according to OECD TG 471 with the registered substance. The outcome of the test is negative;
- An *In vitro* Mammalian Cell Gene Mutation Test according to OECD TG 476 with the registered substance. The outcome of the test is negative; and
- An *In vitro* Mammalian Cell Micronucleus Test performed according to OECD TG 487 with the registered substance that shows positive results: *"The test item induced chromosome damage, or damage to the cell division apparatus, in cultured mammalian somatic cells, using L5178Y TK+/- mouse lymphoma cells in the absence of rat metabolizing system. In the presence of metabolic activation, the test item did not induce any chromosome damage, or damage to the cell division apparatus, in L5178Y TK+/- cultured mouse lymphoma cells."* The positive results indicate that the substance is inducing chromosomal aberrations under the conditions of the tests.

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations is not available for the registered substance. Consequently, there is an information gap.

Hence, you have submitted a testing proposal for a Mammalian Erythrocyte Micronucleus Test (OECD TG 474).

ECHA notes that the proposed test is an appropriate test to further investigate effects on chromosomal aberrations *in vivo* as described in the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.7.1. and figure R.7.7-1 if the test substance or its metabolite(s) will reach the target tissue as specified in the respective test method (OECD TG 474).

However, ECHA further notes that according to the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.7.6.3, the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) is suitable to follow up positive *in vitro* result for chromosomal aberrations for substances of low systemic bioavailability and/or high reactivity. Hence, ECHA considers that this test is also appropriate to address the concern. Therefore, ECHA provides you the choice to perform one of those tests.

You proposed testing in rats by the oral route. According to the test method OECD TG 474, the test shall be performed in mice or rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate. According to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

Therefore, pursuant to Article 40(3) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision:
In vivo mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice or rats, oral route; or *In vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

Notes for your consideration

According to paragraph 10 of the OECD TG 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*". Additionally, according to paragraph 48 (d) of the OECD TG 474, a negative test result can be considered reliable if "*Bone marrow exposure to the test substance(s) occurred*". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then it may not be an appropriate test to meet the information requirements under the REACH Regulation and ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

In case you decided to perform the comet assay, you may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects.

This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

You are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

2. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route is low (maximum 1.6 mg/m^3). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You proposed testing in rats. According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408).

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

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

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation.

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

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. 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 the rat or rabbit as a first species.

You proposed testing by the oral route.

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 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 5 August 2013.

ECHA held a third party consultation for the testing proposal for sub-chronic toxicity (90-days) and from 18 September 2014 until 3 November 2014.

ECHA held a third party consultation for the testing proposal for Reproductive toxicity (pre-natal developmental toxicity) from 18 November 2014 until 2 January 2015.

ECHA held a third party consultation for the testing proposal for Genetic toxicity in vivo from 3 February 2016 until 21 March 2016.

ECHA did not receive information from third parties.

This decision does not take into account any updates after **8 August 2016**, 30 calendar days after the end of the commenting period.

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

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

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the 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 the Member States.

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.