Final decision: TPE-D-0000002587-66-03/F Helsinki, 29 January 2013

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 1,1'-isopropylidenebis(p-phenyleneoxy)dipropan-2-ol, CAS No 116-37-0 (EC No 204-137-9), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12 (1)(e) thereof for 1,1'-isopropylidenebis(p-phenyleneoxy)dipropan-2-ol, CAS No 116-37-0 (EC No 204-137-9), by [redacted] (Registrant).

- Mammalian erythrocyte micronucleus test (OECD 474),
- 90-day oral toxicity study (OECD 408)
- Developmental toxicity / teratogenicity study (OECD 414) and
- Daphnia magna reproduction test (OECD 211).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 2 November 2012, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

On 5 October 2011, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 16 January 2012 until 01 March 2012. ECHA did receive information from third parties (see section III below).

On 19 June 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 13 July 2012 ECHA received comments from the Registrant

ECHA considered the Registrant's comments received.
On basis of the comments, Section II was amended. The Statement of Reasons (Section III)

was changed accordingly.

On 2 November 2012 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408);
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414); and
3. *In vivo mammalian erythrocyte micronucleus test* species and route to be specified by the Registrant (Annex IX, 8.4, test method EU B.12/OECD 474) and to use the FISH coloration technique at all dose levels to distinguish between micronuclei containing acentric fragments and those containing whole chromosomes.
4. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **29 January 2015** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall consider submitting a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Sub-chronic toxicity

a) Examination of the testing proposal

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.

The Registrant proposed testing by the oral route. The physico-chemical properties of the substance may suggest a significant rate of absorption through the skin. However, no toxicity was observed in the acute dermal toxicity test at lower doses than in the oral test and no systemic effects or other evidence of absorption was observed in skin and eye irritation studies. Therefore ECHA considers that testing by the oral route is appropriate.

The Registrant did not specify the species to be tested. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below (see section III, 5. Consideration of third party information) the information provided by third parties does not fulfil Annex XI requirements.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

2. Pre-natal developmental toxicity

a) Examination of the testing proposal

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.

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below (see section III, 5. Consideration of third party information) the information provided by third parties does not fulfil Annex XI requirements.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.
When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

3. *In vivo* mammalian erythrocyte micronucleus test

a) Examination of the testing proposal

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

An appropriate *in vivo* somatic cell genotoxicity study is part of the information requirements as laid down in Annex IX, section 8.4. of the REACH Regulation, if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and if there are no results available from an *in vivo* study already. ECHA notes that in an *in vitro* chromosome aberration test with human lymphocytes available in the registration dossier, a dose-dependent increase in the number of polyploid cells was noted with and without the use of a metabolic activation system. Therefore, the information on the above-mentioned 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 generate the data for this endpoint.

Based on the above, ECHA agrees with the registrant that a test is necessary in order to fulfil the missing data requirement. In his comments on ECHA's draft decision the Registrant brought forward aguments previously not mentioned with respect to the original testing proposal. The Registrant stated that a mammalian erythrocyte micronucleus test (OECD 474) coupled with detection of the centromeric region of chromosomes by using a fluorescent in-situ hybridisation (FISH) technique is an appropriate in vivo test to detect aneuploidy. According to ECHA Guidance on information requirements and chemical safety assessment, R.7A, May 2008, the in vivo mammalian erythrocyte micronucleus test has the potential to detect both clastogenic and aneugenic chemicals. Furthermore, EU method B.12 (OECD 474) includes the option to use techniques such as FISH to distinguish between micronuclei of different origin (whole chromosomes or acentric fragments).
Micronuclei can either contain a product of chromosome breakage (acentric fragments) or whole chromosomes. A significant increase in micronuclei containing whole chromosomes indicates aneugenicity, whereas a significant increase in micronuclei containing acentric fragments indicates clastogenicity. The conventional micronucleus assay cannot distinguish between these two types of micronuclei, whereas the FISH technique can distinguish between micronuclei containing acentric fragments and those containing whole chromosomes, thus having the potential to detect aneuploidy. On the basis of the newly presented arguments ECHA reconsidered its initial approach as communicated in its draft decision to the Registrant to request an *in vivo* mammalian bone marrow chromosome aberration test and accepted the modified testing proposal of the Registrant.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below (see section III, 5. Consideration of third party information) the information provided by third parties does not fulfil Annex XI requirements.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study: *In vivo* mammalian erythrocyte micronucleus test, species and route to be specified by the Registrant (Annex IX, 8.4, test method EU B.12/OECD 474), and to use the FISH coloration technique at all dose levels to distinguish between micronuclei containing acentric fragments and those containing whole chromosomes.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

4. Long-term toxicity testing on aquatic invertebrates

a) Examination of the testing proposal

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

Long-term toxicity testing on invertebrates is a standard information requirement as laid down in Annex IX, 9.1.5. of the REACH Regulation. Column 2 of Section 9.1. of Annex IX further indicates that this information requirement must be fulfilled unless the chemical safety assessment leads to the conclusion that the test is not needed. 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.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. According to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

b) Outcome

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, the Registrant is required to carry out the proposed study: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) using the registered substance.

5. Consideration of third party information

A third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for evaluation of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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