ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 22 November 2019

Addressee: [redacted]

Decision number: CCH-D-2114489551-41-01/F
Substance name: 4,4'-Isopropylidenediphenol, ethoxylated
EC number: 500-082-2
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09/02/2018
Registered tonnage band: 100-1000 (Lead) and over 1000 (Joint registration)

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 cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **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, provided that the study requested under 1. has negative results;**

3. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method: EU C.7./OECD TG 111) with the registered substance;**

4. **Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25./OECD TG 309) at a temperature of 12 °C with the registered substance;**

5. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance.**

You are required to submit the requested information under points *1, 2 and 3 (*In vitro cytogenicity study in mammalian cells or In vitro micronucleus study, In vitro gene mutation study in mammalian cells provided that the study requested under 1 has negative results and Hydrolysis as a function of pH) in an updated registration dossier by ***30 November 2020***.

You are required to submit the requested information under points 4 and 5 (Simulation testing on ultimate degradation in surface water and Identification of degradation products) in an updated registration dossier by ***31 May 2021***. 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 and 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, has to 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 **Claudio Carlon**, Head of Unit, Hazard Assessment

[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

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

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An "In vitro cytogenicity study in mammalian cells or an in vitro micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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 an In Vitro Mammalian Chromosome Aberration Test conducted according to OECD TG 473 and GLP (study report 2010). However, this study does not provide the information required by Annex VIII, Section 8.4.2., because there are contradictions between the results and conclusions on OECD 473 study provided in the IUCLID Section 7.6.1. Under the test results you indicate that genotoxicity was negative with and without metabolic activation. However, in the conclusions you state "*ambiguous with metabolic activation - Marginally significant at limit of toxicity; positive without metabolic activation - Only at limit of toxicity tolerance; Increase in chromatid gaps and exchange seen in high dose replicates. Not certain if this is a result of toxicity, or true mutagenic effect.*" The study results are not presented in a quantitative manner (e.g. data not summarised in a tabulated form) in the study summary while a more detailed report is provided as an attachment in IUCLID section 7.6.1. in Japanese. Hence, ECHA cannot fully assess the validity of the results and the conclusion provided in the study record.

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 chromosome aberration test (test method OECD TG 473) and the in vitro mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. 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: In vitro mammalian chromosome aberration test (test method: OECD TG 473) or in vitro mammalian cell micronucleus study (test method: OECD TG 487).

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

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.
You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* gene mutation study in

mammalian cells (OECD TG 476) with the analogue substance 4,4'-Isopropylidenediphenol, propoxylated, 1 - 4.5 moles propoxylated (EC no 500-097-4).

A. Grouping of substances and read-across approach

Legal requirements for the read-across

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration. The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

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[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

Information you provided

You have provided a read-across documentation in the study record for in vitro gene mutation in mammalian cells (IUCLID Section 7.6.1) and in the endpoint summary (IUCLID Section 7.6).

You use the following arguments to support the prediction of properties of the registered substance from data for source substance: "*Read across from BPA 5PO to BPA 1-4.5EO is considered justifiable in this endpoint as the weight of evidence across the genetic toxicity studies conducted on the BPA EO and the BPA PO show agreeable results. The BPA PO and BPA EO have common constituents, breakdown products and precursors, and are of a similar chemical class. The BPA PO and BPA EO substances are expected to behave the same in the body and the key component for genotoxicity will be the aromatic parts of the molecules*"

As an integral part of this prediction, you propose that the source and registered substance have structural similarity ("*common constituents, breakdown products and precursors, and are of a similar chemical class*") and similar toxicological properties ("*expected to behave the same in the body and the key component for genotoxicity will be the aromatic parts of the molecules*") for the above-mentioned information requirement. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Firstly, your proposed adaptation argument is that the similarity in chemical structure between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for the endpoint of genetic toxicity. Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why the prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

Secondly, there are differences in the constituents of the registered and source substance. These differences could have a potential impact on the toxicity profile. However, you did not provide any considerations whether these differences could affect the possibility to predict properties of the registered substance for the endpoint of genetic toxicity.

Thirdly, you claim that the toxicological properties of the source and registered substances are similar with respect to the genotoxicity: "*the weight of evidence across the genetic toxicity studies conducted on the BPA EO and the BPA PO show agreeable results*" . However, the data you have provided does not allow to reach such a conclusion, as there is no relevant and appropriate information on both target and source substances to allow comparison of toxicological properties with respect to the genotoxicity. In particular, you have provided two in vitro gene mutation studies in bacteria (OECD TG 471 and GLP) with the registered (target) substance with a negative result (2010, 2012) but there is no comparable data on the source provided. Additionally, you have provided a study record for an in vitro chromosome aberration study in mammalian cells (OECD TG 473 and GLP) with the registered (target) substance (2010). However, it indicates an ambiguous outcome, because there are contradictions between the results and conclusions, which prevent considering this study as valid, as described under point 1 in this appendix. You have also provided one in vitro gene mutation study in mammalian cells (OECD TG 476 and GLP) with

the analogue (source) substance with a negative result (2010). However, the reporting of the OECD TG 476 study is deficient as no information on the test substance concentrations is provided, and also cytotoxicity and the choice of top concentration is not specified. Therefore, this study does not allow for comparison of toxicological properties. Additionally, due to the above mentioned deficiencies of the source substance data, the specific requirements of Annex XI, Section 1.5. of the REACH Regulation are not fulfilled: in particular the data provided is not adequate for the purpose of classification and labelling and/or risk assessment and no adequate and reliable documentation of the applied method is provided.

Fourthly, you claim that the source and registered substances "*are expected to behave same in the body and the key component for genotoxicity will be the aromatic parts of the molecules*". However, you did not provide any information on toxicokinetics including the common breakdown products and the possible metabolic pathways.

Your hypothesis based on structural similarity and toxicological properties has not been proven and therefore you have not established why the prediction is reliable for the human health end-point for which the read across is claimed.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for the source substance. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Therefore, your adaptation of the information requirement is rejected.

B. Information requests

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Adequate information on in vitro gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under 1 has negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

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) provided that the study requested under 1 has negative results.

3. Hydrolysis as a function of pH (Annex VIII, 9.2.2.1)

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 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.

The technical dossier contains the following waiver: *'According to [redacted] (1993), [redacted] (2000) and [redacted] (1990) the test substance does not contain any functional groups sensitive to hydrolysis. Therefore, this study does not need to be performed.'*

Although the ether linkages in the substance can be expected not to be prone to facile hydrolysis, it cannot be concluded without experimental evidence that there is no hydrolysis under environmentally relevant conditions. ECHA notes that the registered substance is ethoxylated Bisphenol A (4,4'-isopropylidenediphenol, EC number 201-245-8), i.e. the two phenyl groups on Bisphenol A are replaced with ethoxy or polyethoxy groups. If there was hydrolysis of these ether linkages, Bisphenol A would be regenerated. Bisphenol A is established as an endocrine disruptor substance. Therefore it is important to establish by means of a hydrolysis test whether Bisphenol A can be released from the registered substance.

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.

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: Hydrolysis as a function of pH (test method: EU C.7/OECD TG 111).

4. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)

"Simulation testing on ultimate degradation in water" is a standard information requirement as laid down in Annex IX, section 9.2.1.2. 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.

You have not provided any study record of simulation testing of the registered substance on ultimate degradation in water in the dossier.

You have sought to adapt this information requirement according to Annex IX, Section 9.2., column 2. You provided the following justification for the adaptation: *'.....further testing on biodegradation should be considered if the chemical safety assessment indicates the need to investigate further the degradation of the substance and its degradation products. Based on the screening study conducted with BPA (1-4.5 EO) it was concluded that the substance is not readily biodegradable but can be concluded to be inherently biodegradable. Furthermore the results from the CSA do not trigger a need for further investigation of biotic degradation as risk for the aquatic and sediment compartment are acceptable in every scenario (RCR < 1). With respect to PBT/vPvB properties the substance is not considered PBT/vPvB and therefore further testing on biodegradation is not triggered.'*

According to Annex IX, Section 9.2.1.2, column 2 of the REACH Regulation, simulation testing on ultimate degradation in surface water does not need to be conducted if the substance is highly insoluble in water or is readily biodegradable.

ECHA notes that based on the information in the technical dossier, the registered substance was not readily biodegradable in an OECD 301B test (13% degradation after 28 days).

Additionally, the registered substance has a water solubility of 697 mg/l at 20ºC as measured in an OECD 105 flask method study and so cannot be considered highly insoluble. Simulation testing can therefore not be omitted based on Annex IX, Section 9.2.1.2, column 2.

The substance has wide dispersive outdoor use from the service life of plastic articles and carbon fibre products containing the substance, so direct release to the environment seems likely.

ECHA notes that there is no information available on the degradation products of the substance and this information has also been requested in this decision under point 5. below.

The simulation test on ultimate degradation in water provides information on the rate of loss of the registered substance under environmentally relevant conditions by primary biodegradation and other environmental transformation processes and information on the resulting environmental transformation products resulting from biodegradation and other transformation processes. The ready biodegradation test and the inherent biodegradation test monitor only ultimate biodegradation (i.e. by carbon dioxide evolution in the OECD 301B tests and by DOC removal in the OECD 302B supporting study) and do not give information on primary degradation or other environmental transformation processes and so cannot be used to inform on the degradation products formed. In addition ECHA notes that as discussed in section 3 (above), there is a potential for release of Bisphenol A by hydrolysis.

ECHA considers that at this stage the chemical safety assessment (CSA) is not complete due to the information gaps addressed in this decision. As a result, the CSA cannot be used to justify that there is no need to investigate further the degradation of the substance and its degradation products.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not 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, Chapter R.7b (version 4.0, June 2017) Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.2.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of the REACH Regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions". The Guidance on information requirements and chemical safety assessment R.7b (version 4.0, June 2017) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3.0 February 2016) indicates 12°C (285K) as the average

environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 309. Therefore, the test should be performed at the temperature of 12°C.

In the OECD TG 309 Guideline two test options, the "pelagic test" and the "suspended sediment test", are described. ECHA considers that the pelagic test option should be followed as that is the recommended option for P assessment. The amount of suspended solids in the pelagic test should be representative of the level of suspended solids in EU surface water. The concentration of suspended solids in the surface water sample used should therefore be approximately 15 mg dw/L. Testing natural surface water containing between 10 and 20 mg SPM dw/L is considered acceptable. Furthermore, when reporting the non-extractable residues (NER) in your test results you should explain and scientifically justify the extraction procedure and solvent used obtaining a quantitative measure of NER.

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: Aerobic mineralisation in surface water – simulation biodegradation test (test method: EU C.25./OECD TG 309); The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study.

Notes for your consideration

Before conducting the requested test[s] you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 4.0, June 2017) and Chapter R.11, Section R.11.4.1.1 (version 3.0, June 2017) on PBT assessment.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the test[s] detailed above are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

5. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX 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.

The biodegradation section in the technical dossier does not contain any information in relation to the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement.

Furthermore, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products. Furthermore, as discussed above (section 3),

ECHA also notes that there is a potential for release of Bisphenol A by hydrolysis and therefore would be a degradation product.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding appropriate and suitable test method, the methods will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the hydrolysis study and/or the simulation testing on ultimate degradation in surface water also requested in this decision, or by some other measure. You will need to provide a scientifically valid justification for the chosen method.

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:

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b., Sections R.7.9.2.3 and R.7.9.4.

Appendix 2: Procedural history

ECHA notes that the tonnage band for one member of the joint submission is 1000 tonnes or more per year.

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 03 September 2018.

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 within 30 days of the notification.

ECHA did not receive any comments within the 30 days.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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 the start of substance evaluation in 2021.

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 requests in this decision, or to otherwise fulfil the information requirements 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 tests 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 tests 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 tests 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 tests to be assessed.