ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 27 May 2019

Addressee: [redacted]

Decision number: CCH-D-2114470768-33-01/F
Substance name: 3,3'-(1,4-phenylenediimino)bis[4,5,6,7-tetrachloro-1H-isoindol-1-one]
EC number: 226-999-5
CAS number: 5590-18-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/09/2018
Registered tonnage band of the lead registrant: 1-10
Joint tonnage band: 10 - 100

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.) of the registered substance;**
   - **Nuclear magnetic resonance or mass spectrum**
2. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.) of the registered substance;**
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) with the registered substance;**
4. **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;**
5. **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 both studies requested under 3. and 4. have negative results;**
6. **and 7. Combined repeated dose toxicity study with the reproductive/ developmental toxicity screening test (Annex VIII, Sections 8.6.1. and 8.7.1.; test method: OECD 422) in rats, oral route with the registered substance.**

You have to submit the requested information in an updated registration dossier by **3 June 2020**. You also have to 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 and advice and further observations are provided in Appendix 3.

Appeal

his 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 Wim De Coen, 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 Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to 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. As mentioned in Section 4.2.1 of the Guidance for identification and naming of substances under REACH and CLP, (version 2.1, May 2017) sufficient spectral data is needed to confirm the structure of a nono-constituent substance and consequently to verify its identity.

The current registration contains Infra-red (IR) and Ultra-violet (UV) spectra. A Nuclear Magnetic Resonance (NMR) Spectrum or Mass Spectrum (MS) is missing in section 1.4 of the IUCLID dossier. A scientifically based justification for not including this information has not been provided.

ECHA points out that the identity of the substance cannot be confirmed based exclusively on the IR and UV and considers that the NMR spectra or the MS are necessary for the identification of the substance. NMR spectroscopic analyses such as a ^{1}H-NMR or a ^{13}C-NMR are powerful tools for structure characterisation and elucidation due to characteristic chemical shifts and spin-spin coupling which also reflect the relative abundance of individual atoms. Alternatively, a mass spectrum can be provided.

Therefore, pursuant to Annex VI, Section 2.3.5 of the REACH Regulation, you are requested to submit an NMR or a MS spectrum generated on the substance subject to the present decision. You shall ensure that the description of the analytical methods used for recording the spectrum are specified in the dossier in such detail to allow the methods to be reproduced, in line with the requirements under Annex VI Section 2.3.7 of the REACH Regulation. You shall ensure that the information is consistent with the information provided throughout the dossier.

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

In your comments to the initial draft decision, you agreed to submit the requested data.

2. High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)

According to Annex VI Section 2.3.6, chromatographic data is required be reported in a registration dossier and this information is required to be sufficient to enable the identity and composition of the substance to be verified.

In the present dossier you have not included information on the chromatographic analytical method(s) used to derive the composition of your substance as reported in IUCLID section 1.2. Also the results of that analysis were not provided.

No justification for the non-inclusion of this information was included in your dossier.

Without chromatographic data it is not possible to establish the identity and concentration levels of the main constituent and impurities required to be reported in the dossier.

You are accordingly requested to provide the description and results of chromatographic methods used to verify the composition of the registered substance as reported in section 1.2. The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed by any calculation made and the results obtained.

For chromatographic methods the following information is expected to be provided:

- Results of analysis: chromatogram and peak table including peak identification, retention times, peak area and area %.
- Description of the method: details of sample/standard preparation, column specification, and identity of carrier gas/eluent and detector type.

You shall ensure that the composition reported in IUCLID section 1.2 of the dossier is consistent with the analytical results obtained.

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

In your comments to the initial draft decision, you agreed to submit the requested data.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments either in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation and/or of predictions generated with the use of QSAR models under Annex XI, Section 1.3 of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your adaptations in general before assessing the individual endpoints (sections 3. and 6).

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for several endpoints, including

- In vitro gene mutation study in bacteria
- Short-term repeated dose toxicity study (28 days)
- Screening for reproductive/developmental toxicity

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. Unambiguous substance identity for both the source substance and the target substance is therefore a prerequisite

for a read-across assessment. 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.

You consider to achieve compliance with the REACH information requirements for the registered substance [3,3'-(1,4-phenylenediimino)bis(4,5,6,7-tetrachloro-1h-isoindol-1-one)] using data of structurally similar substances 1,2-Bis(tetrabromo phthalimide)ethane (CAS No 32588-76-4; EC No 251-118-6), Octachlorodibenzodioxin (CAS No 3268-87-9, EC No 694-813-3), and Tetrachlorophthalic Anhydride (CAS 117-08-8; EC No 204-171-4) (hereafter the 'source substances').

However, there is no documentation for the read-across. Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances.

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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).

In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance.

Hence, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substance. Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance.

Qualitative or Quantitative structure-activity relationship ((Q)SAR)

You have sought to adapt information requirements by predictions generated with the use of QSAR models under Annex XI, Section 1.3. of the REACH Regulation, for several endpoints, including

- In vitro gene mutation study in bacteria
- Short-term repeated dose toxicity study (28 days)
- Screening for reproductive/developmental toxicity

For the use of (Q)SAR models, according to Annex XI, Section 1.3., the results obtained from valid (Q)SAR models may be used instead of testing when the following conditions are met[4]:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

In the technical dossier you have provided automated reports generated with the OECD QSAR Toolbox for the purpose of predicting genotoxicity and for predicting of NOAEL values for repeated-dose toxicity and toxicity to reproduction of the registered substance.

ECHA notes that you have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA therefore concludes that the proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3. and is therefore rejected.

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

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.

[4] 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for *In vitro* gene mutation studies in bacteria (OECD TG 471) with the analogue substances 1,2-Bis(tetrabromo phthalimide)ethane (EC No 251-118-6) and Octachlorodibenzodioxin (EC No 694-813-3). Furthermore, you have indicated "calculation" in the administrative section of the endpoint study record in the technical dossier for *In vitro* gene mutation study in bacteria for predicting the properties of the registered substance. In addition, you have claimed predicting the property by estimation using a (Q)SAR model.

However, as explained above in Appendix 1, sections "Grouping of substances and read-across approach" and "Qualitative or Quantitative structure-activity relationship ((Q)SAR)" of this decision, your adaptations of the information requirement are rejected.

In your comments to the initial draft decision, you explain that you already have test information on the registered substance and on source substances. However, this information is not included in the dossier and based on the limited details included in your comments, ECHA cannot evaluate the information.

Hence, 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).

4. 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.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

In your comments to the initial draft decision, you explain that you already have test information on the registered substance and on source substances. However, this information is not included in the dossier and based on the limited details included in your comments, ECHA cannot evaluate the information.

Hence, 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).

5. 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.

ECHA notes that the registration dossier does not contain study records for this endpoint. 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 both studies requested under 3. and 4. have negative results. ECHA set the deadline for provision of the information to allow for sequential testing. You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

In your comments to the initial draft decision, you stated that the study does not need to be conducted since there are no indications that the substance would be genotoxic. However, no valid mutagenicity tests are included in the dossier or your comments, and it is therefore not possible to conclude that the substance is not mutagenic.

Hence, 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) provided that both studies requested under 1. and 2. have negative results.

6, 7. Combined repeated dose toxicity study with the reproductive/ developmental toxicity screening test (Annex VIII, Sections 8.6.1. and 8.7.1.)

A "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. of the REACH Regulation and a "Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. Adequate information on those endpoints needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt the information requirement for a short-term repeated dose toxicity study according to Annex XI, Section 1.5. and Annex XI, Section 1.3 of the REACH Regulation by providing a study record for short-term repeated dose toxicity with the analogue substance Tetrachlorophthalic Anhydride (EC No 204-171-4), and by predicting a NOAEL value for the registered substance by estimation using a (Q)SAR model. However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" and "Qualitative or Quantitative structure-activity relationship ((Q)SAR)" of this decision, your adaptations of the information requirement are rejected.

Furthermore, you have sought to adapt the information requirement for a "Screening for reproductive/developmental toxicity" according to Annex XI, Section 1.5. and Annex XI, Section 1.3. of the REACH Regulation by providing study records for reproductive and chronic toxicity with the analogue substance Tetrachlorophthalic Anhydride (EC No 204-171-4), and by predicting a NOAEL value for the registered substance by estimation using a (Q)SAR model. However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" and "Qualitative or Quantitative structure-activity relationship ((Q)SAR)" of this decision, your adaptations of the information requirement are rejected.

In your comments to the initial draft decision, you explain that you already have test data on source substances which are not further identified. However, this information is not included in the dossier and based on the limited details included in your comments, ECHA cannot evaluate the information.

As explained above, the information provided on those endpoints for the registered substance in the technical dossier does not meet the information requirement. Consequently there are information gaps and it is necessary to provide information for those endpoints.

REACH Annex VIII, Section 8.6.1. refers to short-term repeated dose toxicity (28 days), which can be tested by the oral route according to the test methods OECD TG 407 or 422, and REACH Annex VIII, Section 8.7.1. refers to screening studies for reproductive/ developmental toxicity according to the test methods OECD TG 421 or 422. OECD TG 422 provides initial information on reproductive toxicity and on sub-acute toxicity. Alternatively, to provide the same information, a separate sub-acute toxicity study (OECD TG 407) and a separate screening study (OECD TG 421) could be performed, which would require more animals. Hence, ECHA considers the test method OECD TG 422 as most appropriate due to animal welfare and proportionality reasons.

According to the test methods OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

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 6.0, July 2017) Chapter R.7a, Section 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: Combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline. You did however not justify this request. Therefore, ECHA has not modified the deadline of the decision.

Appendix 2: Procedural history

ECHA notes that the tonnage band for one member of the joint submission is 10 to 100 tonnes 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 24 July 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.

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

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 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 requests in this decision 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 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.