~~Confidential~~

Helsinki, 02 June 2023

**Addressees**
Registrant as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
28/03/2018

**Registered substance subject to this decision ("the Substance")**
Substance name: p-phenylenebis(methylamine)
EC number/List number: 208-719-3

**Decision number:** Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

## DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***10 June 2024***.

Requested information must be generated using the Substance unless otherwise specified.

### Information required from all the Registrants subject to Annex VII of REACH

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020))

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

The reasons for the requests are explained in Appendix 1.

### Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee of the decision and its corresponding information requirements based on registered tonnage band are listed in Appendix 3.

### How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

**Appeal**

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

**Failure to comply**

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the requests
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the request(s)

**Contents**

**Reasons common to several requests**

*0.1. Read-across adaptation rejected*

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5.:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. 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.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

*0.1.1. Predictions for ecotoxicological properties*

5 You provide a read-across justification document in IUCLID Section 6.1.3 and 6.1.5.

6 You predict the properties of the Substance from information obtained from the following source substance:

- MXDA, 1,3-benzenedimethanamine, EC 216-032-5

7 You provide the following reasoning for the prediction of ecotoxicological properties: *"A structural analogue is a source chemical whose physico-chemical and toxicological properties are likely to be similar to the target chemical as a result of structural similarity. The similarity may be based on a common functional group or a common precursor and/or breakdown product that results via physical or biological processes (metabolic pathway similarity)."*

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issues with the prediction of ecotoxicological properties:

*0.1.1.1. Missing supporting information to compare properties of the substances*

10 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

11 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance causes the same type of effects. In this context, relevant,

reliable and adequate information allowing to compare the properties of the substance is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance.

12 To support your hypothesis on similar ecotoxicological effects, you have provided a short-term toxicity study on Daphnia and a study on toxicity to aquatic algae with the source substance. In addition, you have provided predictions (ECOSAR) of a short-term toxicity to Daphnia and toxicity aquatic algae with the source substance and the Substance.

13 ECHA take notes that the only bridging information provided in support of the predictions are the QSAR predictions based on ECOSAR. However, this information is not considered as a reliable basis to compare the properties of the Substance and the selected analogue substance for the following reasons:

*0.1.1.1.1. Lack of documentation of the model (QMRF)*

14 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

15 You have not provided information about the model.

16 In absence of such information, ECHA cannot establish that the model can be used to provide reliable supporting information to your read-across hypothesis.

*0.1.1.1.2. Lack of documentation of the prediction (QPRF)*

17 Guidance on IRs and CSA R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

18 You have not provided information about the prediction.

19 In absence of such information, ECHA cannot establish that the model can be used to provide reliable supporting information to your read-across hypothesis.

20 In the absence of adequate information to support your read-across hypothesis, you have not established that the Substance and the source substance are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

*0.1.1.2. Inadequate or unreliable study on the source substance*

21 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) be adequate for the purpose of classification and labelling and/or risk assessment;

(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

22 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement sections 2 and 3. Therefore, no reliable predictions can be made for these information requirements.

*0.1.2. Conclusion on the read-across approach*

23 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

**Reasons related to the information under Annex VII of REACH**

## 1. *In vitro* gene mutation study in bacteria

24 An in vitro gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

### *1.1. Information provided*

25 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) an *in vitro* gene mutation study in bacteria (1998) with the Substance;

(ii) an *in vitro* gene mutation study in bacteria (1997) with the Substance.

### *1.2. Assessment of the information provided*

#### *1.2.1. Weight of evidence adaptation is rejected*

26 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

27 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

28 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

##### *1.2.1.1. Lack of documentation justifying the weight of evidence adaptation*

29 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

30 You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

31 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

32 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VII, Section 8.4.1. includes similar information that is produced by the OECD TG 471 with a design as specified in this decision. OECD TG 471 requires the study to investigate the following key element:

- detection and quantification of gene mutation (base pairs, substitution or frameshift) in cultured bacteria including data on the number of revertant colonies.

33 The sources of information (i) and (ii) may provide relevant information on the above mentioned key parameter.

34 However, the reliability of these sources of information is significantly affected by the following deficiency:

*1.2.1.2. The provided studies are not reliable due to technical deficiencies*

35 To inform on in vitro gene mutation in bacteria in the context of the weight of evidence adaptation, a study must normally be conducted under conditions that are consistent with the specifications of the OECD TG 471. Therefore, the following specifications must be met:

a) triplicate plating is used at each dose level;

b) the mean number of revertant colonies per plate is reported for the treated doses and the controls;

36 In studies (i) and (ii):

a) only two replicates were used at each dose level without any scientific justification. Without a sufficient number of replicates, the variability of the study results cannot be adequately assessed;

b) the mean number of revertant colonies per plate for the treated doses and the controls was not reported. Without these data:

- the mean number of revertant colonies of the treated plates and the negative control plates cannot be compared and the absence (or presence) of significant difference between them cannot be confirmed;
- the mean number of revertant colonies in the positive controls cannot be compared with the negative control values to confirm appropriateness of the positive controls and effectiveness of the metabolic activation systems;
- the spontaneous background mutant frequency in each strain and their consistency with literature values cannot be evaluated;
- the dose-response relationship cannot be assessed;
- the relevance of the positive findings with TA 104 in study (ii) cannot be evaluated;
- the reproducibility of study results cannot be assessed.

37 Due to the significant deficiencies identified above, the provided studies cannot be considered reliable sources of information that could contribute to the conclusion on this key parameter investigated by the required study.

38 In summary, the sources of information (i) and (ii) provide relevant information on detection and quantification of gene mutation. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for in vitro gene mutation study in bacteria.

39 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for in vitro gene mutation study in bacteria.

40 Based on the above, your adaptation is rejected.

41 Therefore, the information requirement is not fulfilled.

*1.3. Specification of the study design*

42 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471) is considered suitable.

## 2. Short-term toxicity testing on aquatic invertebrates

43 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

### *2.1. Information provided*

44 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substance:

(i) a short-term toxicity study on *Daphnia magna* (1995) with the source substance 1,3-benzenedimethanamine, EC 216-032-5, MXDA.

### *2.2. Assessment of the information provided*

#### *2.2.1. Read-across adaptation rejected*

45 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified the following issue.

##### *2.2.1.1. Inadequate or unreliable study on the source substance*

46 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 202. Therefore, the following specifications must be met:

*Characterisation of exposure*

a) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;

*Reporting of the methodology and results*

b) the age of the test animals is reported;

c) the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;

d) the dissolved oxygen at least at the beginning and end of the test is reported.

47 In study (i):

*Characterisation of exposure*

a) no analytical monitoring of exposure was conducted

*Reporting of the methodology and results*

b) the age of the test animals is not reported;

c) tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported;

d) the dissolved oxygen measured at least at the beginning and end of the test is not reported.

48 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, analytical monitoring was not conducted. Therefore, you have not demonstrated that the test organisms were adequately exposed to the test material during the exposure phase.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. You do not report the age of the test animals at the beginning of the test. The test is designed to be performed with neonates that are <24 hours old and if there is any deviation from this, the sensitivity of the test may have changed. Also, data on immobilised daphnids in replicates is not reported and all details on the immobility are needed to assess e.g. variability between the replicates and the reliability of the calculated effective concentrations. In addition, dissolved oxygen concentration is not reported. Since abnormal oxygen content of the test medium may influence behaviour of daphnids and thereafter test material toxicity in the test, the oxygen content must be reported that the standard conditions defined in test guideline can be confirmed.

49 On this basis, the specifications of OECD TG 202 are not met.

50 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter of the corresponding OECD TG.

51 Therefore, this information requirement is not fulfilled.

## 3. Growth inhibition study aquatic plants

52 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

### *3.1. Information provided*

53 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) Growth inhibition study on aquatic plants/algae (1995) with the source substance 1,3-benzenedimethanamine, EC 216-032-5 / MXDA;

### *3.2. Assessment of the information provided*

#### *3.2.1. Read-across adaptation rejected*

54 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified the following issue.

*3.2.1.1. Inadequate or unreliable study on the source substance*

55 To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

*Characterisation of exposure*

a) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;

*Reporting of the methodology and results*

b) the test conditions are reported (*e.g.*, composition of the test medium);

c) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

56 In study (i):

*Characterisation of exposure*

a) no analytical monitoring of exposure was conducted;

*Reporting of the methodology and results*

b) on the test conditions, you have not specified composition of the test medium;

c) tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

57 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, analytical monitoring was not conducted. Therefore, you have not demonstrated that the test organisms were adequately exposed to the test material during the exposure phase.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported the composition of the test medium. The composition of the test medium is critical as it may impact the sensitivity of the test. Furthermore, in the absence of tabulated data on the algal biomass, it is not possible to assess whether the validity criteria of the test guideline were met and to verify the interpretation of the study results.

58 On this basis, the specifications of OECD TG 201 are not met.

59 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

60 Therefore, the information requirement is not fulfilled.

**References**

The following documents may have been cited in the decision.

***Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)***

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

***Guidance on data-sharing***; ECHA (2017).
**Guidance for monomers and polymers**; ECHA (2012).
**Guidance on intermediates;** ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

***Read-across assessment framework (RAAF)***

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

**Appendix 2: Procedure**

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 14 June 2022.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 6 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

ECHA did not receive any comments within the commenting period.

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: Addressee(s) of this decision and their corresponding information requirements**

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

| Registrant Name | Registration number | Highest REACH Annex applicable to you |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

## Appendix 4: Conducting and reporting new tests for REACH purposes

### 1. Requirements when conducting and reporting new tests for REACH purposes

### 1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

### 1.2. Test material

(1) Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested, in this case purity and presence of impurities.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).

References to Guidance on REACH and other supporting documents can be found in Appendix 1.

[2] https://echa.europa.eu/practical-guides