~~Confidential~~

Helsinki, 02 June 2023

Addressees
Registrants of [redacted] SIEF JS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
22/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: m-phenylenebis(methylamine)
EC number/List number: 216-032-5

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 ***09 March 2027***.

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

Information required from all the Registrants subject to Annex VIII of REACH

1. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei

2. Simulation testing on ultimate degradation in surface water, also requested below (triggered by Annex VIII, Section 9.2.)

3. Identification of degradation products, also requested below (triggered by Annex VIII, Section 9.2.)

4. Bioaccumulation in aquatic species, also requested below (triggered by Annex VIII, Section 9.3., Column 2.)

Information required from all the Registrants subject to Annex IX of REACH

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

6. Identification of degradation products (Annex IX, Section 9.2.3.; test method: EU C.25/OECD TG 309)

7. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: EU C.13./OECD TG 305, aqueous exposure)

Information required from all the Registrants subject to Annex X of REACH

8. Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit)

9. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:
    - Ten weeks premating exposure duration for the parental (P0) generation;
    - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
    - Cohort 1A (Reproductive toxicity);
    - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning; and
    - Cohort 3 (Developmental immunotoxicity).

    You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified

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 addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

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. In addition, the studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in this Appendix.

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 related to the information under Annex VIII of REACH

1. *In vitro* micronucleus study

1 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

1.1. Information provided

2 You have provided:

(i) an *in vitro* cytogenicity study in mammalian cells according to OECD TG 473 (key study, 1989) with the Substance;

(ii) an *in vitro* cytogenicity study in mammalian cells according to OECD TG 473 (supporting study, 1996) with the Substance.

3 In addition, you have provided an in vivo micronucleus test (1989) with the Substance. This test does not correspond to the test required under this information requirement. However, you do not provide any justification as to why this test could contribute to the fulfilment of this information requirement.

1.2. Assessment of the information provided

1.2.1. The provided studies do not meet the specifications of the test guidelines

4 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, for a study according to OECD TG 473, the following specifications must be met:

b) the positive controls induce responses compatible with those generated in the historical positive control database;

In studies (i) and (ii), the historical positive control data was not provided.

c) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

In study (ii), the historical negative control data was not provided.

d) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported;

In studies (i) and (ii), data on the cytotoxicity for the treated and control cultures were not reported.

e) to conclude on a negative outcome, a negative response is obtained in all three experimental conditions described in paragraph 28 of OECD TG 473, using a short-term treatment with and without metabolic activation and long-term treatment without metabolic activation.

In study (ii), two experimental conditions described in paragraph 28 of OECD TG 473 (i.e. a short-term treatment with metabolic activation and a long-term treatment without metabolic activation) are missing to conclude on a negative outcome.

5 The studies provided do not cover the specifications required by the OECD TG 473.

6 Therefore, the information requirement is not fulfilled.

1.3. Specification of the study design

7 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

1.3.1. Assessment of aneugenicity potential

8 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

9 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

2. Simulation testing on ultimate degradation in surface water

10 Under Annex VIII, Section 9.2., Column 2, further information on degradation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the degradation of the substance.

2.1. Triggering of the information requirement

11 More specifically, this information requirement is triggered in case where additional information on degradation as set out in Annex XIII, point 3.2.1, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex. This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as it is not readily biodegradable (i.e. <70 % degradation in an OECD 301B);
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as for some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to

protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid;

- it potentially meets the T criteria set in Annex XIII: NOEC or EC_{10} < 0.01 mg/L or classification as carc. 1A or 1B, muta. 1A or 1B, repro. 1A, 1B or 2, or STOT RE 1 or 2.

12 Your registration dossier provides the following:

- the Substance is not readily biodegradable (49% degradation after 28 days in OECD TG 301B);
- the Substance is an ionisable substance and therefore high potential for bioaccumulation cannot be excluded based on available information.

13 Furthermore:

- it is not possible to conclude on the bioaccumulation potential of the Substance (see Request 7. of this decision), and
- it is not possible to conclude on the toxicity of the Substance see requests 8 and 9 of this decision).

14 Under section 2.3 of your IUCLID dossier, you conclude that the Substance is not P/vP and not B/vB. In support of your conclusion you provide the following justifications:

- "Based on substance characteristics and available experimental information the substance is not expected to persist in the environment";
- "*The substance has a log Kow of 0.18, which is clearly below the threshold value relevant for classification as bioaccumulative. This is confirmed by measured bioconcentration factors showing the low potential of the substance to bioaccumulate in aquatic organisms*"

15 However, as explained above the Substance may be persistent based on the results of the available ready biodegradability study and your justification does not provide any additional information to support that the Substance does not meet the P/vP criteria. Furthermore, as explained above, the bioaccumulation potential of the Substance may not be solely driven by lipophilicity and therefore, log Kow is not a reliable criterion to exclude that the Substance may be B/vB. ECHA notes that the data on bioconcentration you referred to are not considered reliable to conclude on Bioaccumulation (see request 7 for details).

16 Therefore, the additional information from your PBT assessment is not adequate to conclude that the Substance is not a potential PBT/vPvB substance.

17 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance. Further, the additional information from your PBT assessment is not adequate to conclude on the PBT/vPvB properties of the Substance.

18 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

2.1. Information requirement not fulfilled

19 The information provided, its assessment and the specifications of the study design are addressed under request 5.

3. Identification of degradation products

20 Under Annex VIII, Section 9.2., Column 2, further information on degradation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the degradation of the substance.

21 Therefore, this information requirement is triggered in case if for example additional information on degradation as set out in Annex XIII, point 3.2.1, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

22 As already explained in request 2., the Substance is a potential PBT/vPvB substance.

23 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

24 Your registration dossier does not include any information on Identification of degradation products.

25 Therefore, the information requirement is not fulfilled.

3.1. Information requirement not fulfilled

26 The information provided, its assessment and the specifications of the study design are addressed under request 6.

4. Bioaccumulation in aquatic species

27 Under Annex VIII, Section 9.3., Column 2, further information on bioaccumulation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the bioaccumulation properties of the substance.

28 More specifically, this information requirement is triggered in case where additional information on bioaccumulation as set out in Annex XIII, point 3.2.2., is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1. of that Annex.

29 As already explained in request 2, the Substance is a potential PBT/vPvB substance.

30 Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

4.1. Information requirement not fulfilled

31 The information provided, its assessment and the specifications of the study design are addressed under request 7.

Reasons related to the information under Annex IX of REACH

5. Simulation testing on ultimate degradation in surface water

32 Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

5.1. Information provided

33 You have adapted this information requirement by using what we understand as an Annex XI, Section 3. (substance-tailored exposure-driven testing). To support the adaptation, you have provided the following information: "*the study does not need to be conducted because exposure of the aquatic compartment is unlikely. For further explanation, see CSR section 9 (Exposure Assessment)*".

5.2. Assessment of the information provided

5.2.1. Substance-tailored exposure-driven testing adaptation rejected

34 Under Annex XI, Sections 3(1) and (2), testing may be omitted based on the exposure scenario(s) developed in the chemical safety assessment (CSR) by providing an adequate and scientifically supported justification based on a thorough and rigorous exposure assessment.

35 You have identified uses for the Substance, and created exposure scenario in the CSR where you claim an absence of release. However, you have not provided any documentation substantiating this statement.

36 Therefore, you have not provided and adequate and scientifically supported justification of an absence of release.

37 Based on the above, your substance-tailored exposure driven testing adaptation under Annex XI, Section 3, is rejected.

38 Therefore, the information requirement is not fulfilled.

5.3. Study design and test specifications

39 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1):

(1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and

(2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

40 You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

41 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

42 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

43 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; Guidance on IRs and CSA, Section R.11.4.1.).

6. Identification of degradation products

44 Identification of abiotic and biotic degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

6.1. Information provided

45 You have not submitted any information on Identification of degradation products.

46 Therefore, the information requirement is not fulfilled.

6.2. Study design and test specifications

47 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

(1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
(2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

48 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported. In addition, identified transformation/degradation products must be considered in the CSA including the PBT assessment.

49 You must obtain this information from the degradation study requested under request 5.

50 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (request 5) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, *e.g.* 20°C) and at higher application rate (*i.e.* > 100 µg/L).

7. Bioaccumulation in aquatic species

51 Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

7.1. Information provided

52 We understand that you intend to adapt this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) an OECD SIDS report (2001) referring to an OECD TG 305 study on the Substance;
(ii) a BCF prediction using the BCFBAF model from EPISUITE (2010).

53 We understand that you intended alternatively to adapt this information requirement by using Column 2 of Annex IX, Section 9.3.2. To support the adaptation, you have provided following justification: "*the study does not need to be conducted because the substance has a low potential for bioaccumulation based on log Kow <=3 and a low potential to cross biological membranes*".

7.2. Assessment of the information provided

7.2.1. Your weight of evidence adaptation is rejected

54 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.

55 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.

56 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.

7.2.1.1. Lack of documentation justifying the weight of evidence adaptation

57 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.

58 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.

59 However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

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

61 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 9.3.2 includes similar information that is produced by the OECD TG 305. OECD TG 305 requires the study to investigate the following key elements:

Key parameters

the study covers the following key parameters:

- the uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2), and/or
- the steady-state bioconcentration factor (BCF_{SS}), and/or
- the kinetic bioconcentration factor (BCF_K), and/or
- the biomagnification factor (BMF).

62 The sources of information (i) and (ii) may provide what ECHA understands as relevant information on BCFss.

63 However, the reliability of these sources of information is significantly affected by the following deficiencies:

7.2.1.2. The reporting of study (i) does not allow conducting an independent assessment of its reliability

64 To information on bioaccumulation in aquatic species, normally a study must comply with the OECD TG 305 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Reporting of the methodology and results

a) adequate information on the test material identity is provided (composition, purity, presence of impurities)
b) the analytical method used for the quantification of the test material in the test solutions and in fish tissues is described. The recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range are reported;
c) mortality of the control fish and the fish in each exposure chamber and any observed abnormal behaviour and adverse effects observed are reported;
d) the lipid content of the fish measured at least before the beginning and at the end of the uptake phase and end of depuration phase, the method used for its determination and the lipid normalisation factor (L_n), if applicable, are reported;
e) individual fish wet weights and total lengths for all sampling intervals are provided and be linked to the analysed chemical concentration for that individual. The data are used to correct the BCF for growth dilution, and the of growth rate constant(s) are provided;
f) tabulated test material concentration data in individual fish (C_f) and water (C_w) (including mean values for test group and control, standard deviation and range, if appropriate) for all sampling times as well as C_w values for the control series (background) are provided.

65 In study (i):

Reporting of the methodology and results

a) -f) none of the information listed above is provided.

66 While this is not explicit from your robust study summary, ECHA assumes that the reported BCF corresponds to a steady state BCF (i.e. BCFss) as the study does not include a depuration phase. However, in the absence of the mandatory information listed under

points a) to f) above, the reporting of the study is not sufficient to conduct an independent assessment of the reliability of the reported BCF estimate.

67 And as a result, this source of information is so severely affected by the issues identified above that it provides little weight to conclude on the information requirement.

7.2.1.3. The provided (Q)SAR is unreliable as the Substance falls outside the applicability domain of the model

68 Under ECHA Guidance R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

69 You have used EPISUITE with module BCFBAF as a model for estimating BCF.

70 The Substance has the following properties related to the estimation of applicability domain: it is ionised at environmental relevant pHs.

71 However, the model used is not validated for ionisable substances.

72 Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model. As a result, this source of information is so severely affected by the issue identified above that it provides little weight to conclude on the information requirement.

7.2.1.4. Conclusion on the weight of evidence adaptation

73 In summary, the sources of information (i) to (ii) provide limited relevant information on Bioconcentration factor. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for Bioaccumulation in aquatic species.

74 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for Bioaccumulation.

75 Based on the above, your adaptation is rejected.

7.2.2. The log K_{ow} is not a valid descriptor of the bioaccumulation potential of the Substance

76 Under Section 9.3.2., Column 2, first indent of Annex IX to REACH, the study may be omitted if the substance has a low potential for bioaccumulation and/or a low potential to cross biological membranes.

77 A low log K_{ow} (i.e. log K_{ow} < 3) on its own may be used to show low potential for bioaccumulation only if the potential for bioaccumulation of the substance is solely driven by lipophilicity. This excludes, for example, situations where the substance is surface active or ionisable at environmental pH (pH 4 – 9).

78 Your registration dossier provides an adaptation stating that the log K_{ow} is < 3 without further explanation.

79 In addition, the Substance is ionised at environmental pHs (pKa of 8.9) which indicates that other partitioning mechanisms may drive bioaccumulation (*e.g.*, binding to protein/cell membranes).

80 Consequently, log K_{ow} is not a valid descriptor of the bioaccumulation potential of the Substance and your adaptation is rejected.

81 Therefore, the information requirement is not fulfilled.

7.3. Study design and test specifications

82 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

83 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

84 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

Reasons related to the information under Annex X of REACH

8. Pre-natal developmental toxicity study in a second species

85 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2.

8.1. Information provided

86 You have adapted this information requirement and provided an "*Expert statement for m-phenylenebis(methylamine)*" attached to IUCLID, Section 7.8.2. which you consider adequate to omit the information requirement.

8.2. Assessment of the information provided

8.2.1. Your justification to omit the study has no legal basis

87 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7., Column 2.

88 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI or Annex X, Section 8.7, Column 2 and ECHA is unable to identify any legal basis that would underpin your intended adaptation.

89 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

8.3. Specification of the study design

90 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study in the first species was carried out by using a rodent species (rat).

91 Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

92 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.2, Column 1).

93 Based on the above, the study must be conducted in rabbits with oral administration of the Substance.

9. Extended one-generation reproductive toxicity study

94 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X, Section 8.7.3. Furthermore Column 2 defines the conditions under which the study design needs to be expanded.

9.1. Information provided

95 You have adapted this information requirement and provided an "[redacted]" attached to IUCLID, Section 7.8.2. which you consider adequate to omit the information requirement.

9.2. Assessment of the information provided

9.2.1. Your justification to omit the study has no legal basis

96 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7., Column 2.

97 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex X, Section 8.7, Column 2 and ECHA is unable to identify any legal basis that would underpin your intended adaptation.

98 Therefore, you have not demonstrated that this information can be omitted, and the information requirement is not fulfilled.

9.3. Specification of the study design

9.3.1. Species and route selection

99 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.3, Column 1).

9.3.2. Pre-mating exposure duration

100 The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

101 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

102 Therefore, the requested pre-mating exposure duration is ten weeks.

9.3.3. Dose-level setting

103 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, paragraph 22; OECD GD 151, paragraph 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

104 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Annex I, Section 3.7.2.4.4. of the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, paragraph 18) in the P0 animals.

105 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending

sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

106 In summary: unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or

(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or

(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or

(4) the highest dose level in P0 animals must follow the limit dose concept.

107 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

108 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

9.3.4. Cohorts 1A and 1B

109 Cohorts 1A and 1B belong to the basic study design and must be included.

9.3.4.1. Splenic lymphocyte subpopulation analysis

110 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, paragraph 66; OECD GD 151, Annex Table 1.3).

9.3.4.2. Investigations of sexual maturation

111 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, paragraph 12 in conjunction with OECD TG 443, paragraph 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

9.3.5. Extension of Cohort 1B

112 If the conditions of Section 8.7.3., Column 2 are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

113 The extension is required, among others, if the use of the Substance is leading to significant exposure of consumers and professionals (Section 8.7.3., Column 2, first paragraph, point (a)) and if there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (Section 8.7.3., Column 2, first paragraph, point (b), third indent).

114 The use of the Substance reported in the joint submission is leading to significant exposure of professionals because the Substance is used by professionals as PROC 1, 2, 3, 4, 7, 8a, 8b, 9, 10, 11, 13, 15.

115 Furthermore, there are indications of one or more modes of action related to endocrine disruption because the following was observed:

- in the sub-acute toxicity study (1996): reddened adrenals in females at 600 mg/kg bw/day, significant increase of relative weight of adrenals in males and females at 600 mg/kg bw/day, histopathological findings in adrenals in males and females at 600 mg/kg bw/day, hypertrophy of the adrenals in females at 600 mg/kg bw/day;
- in the screening study for reproductive toxicity (1999): increased absolute and relative weight of the adrenals in males at 450 mg/kg bw/day, diffuse hyperplasia in the adrenal cortex in males and females. In addition, increased relative weight of the tested was observed.

116 For the reasons stated above, the Cohort 1B must be extended.

117 Organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, paragraphs 67 and 72) because there is a concern for reproductive toxicity/endocrine activity indicated by the toxicity-triggers to extend the Cohort 1B.

118 The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151.

9.3.6. Cohort 3

119 The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

120 Existing information on the Substance itself derived from the available studies shows the following:

- in the sub-acute toxicity study (1996): atrophy of the thymus and spleen in females at 600 mg/kg bw/day, reduction in lymphocyte ratio in males at 600 mg/kg bw/day, increase in leukocyte count in males and females at 600 mg/kg bw/day, and increase in segmented neutrophil ratio in differential leukocyte count in males at 600 mg/kg bw/day;
- in the screening study for reproductive toxicity (1999): decreased absolute weight of the thymus in males, and atrophy of the thymus in females at 450 mg/kg bw/day. In addition, one female showed atrophy of the spleen at 150 mg/kg bw/day;
- in the skin sensitisation studies (local lymph node assay and guinea pig maximisation study): skin sensitisation potential.

121 To summarize, the effects in the thymus were consistent between the sub-acute study and the screening study. These effects were further reflected in the lymphocytes ratio in the sub-acute study. In addition, the skin sensitisation potential shows immunostimulation at a local level and it further supports that the immune system is a target system for the Substance. Therefore, the Substance itself shows dysregulation of the immune system.

122 Because the immune system is under development in the post-natal period, the dysregulation of the immune system could have a more severe impact on developing organisms.

123 For the reasons stated above, the developmental immunotoxicity Cohort 3 must be conducted.

9.3.7. Further expansion of the study design

124 No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity were identified. However, you may expand the study by including Cohorts 2A and 2B if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Annex IX/X, Section 8.7.3., Column 2. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

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

The information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6.) is not addressed in this decision. This is because information that will be generated from the studies requested in the present decision is needed:

- to inform on the potential endocrine disrupting properties of the Substance; and
- to decide on the most appropriate test(s) to meet the information requirement.

This information requirement may be addressed in a separate decision at a later stage.

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 12 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.

In the comments you explain that you have no comments on the requests and that you receive no comments from the other members of the joint submission. Therefore, ECHA did not amend the requests.

In the comments you explain that you have doubts that the deadline of the decision (i.e., 42 months) would provide enough time to perform the requested studies considering the current workload of labs you are in contact with. However, you did not explicitely request to extend the deadline and you did not provide documentary evidence that the extension is justified by constraints on lab capacity. As explained above, the deadline was already exceptionally extended by 12 months to take into account longer lead times in contract research organisations.

On this basis, ECHA has not modified the deadline.

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments and referred the modified draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-82 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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]
[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

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(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 variation in compositions reported by all members of the joint submission,
- 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.

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

- 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 and whether it is suitable for use by all members of the joint submission.

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).

2. General recommendations for conducting and reporting new tests

2.1. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult Guidance on IRs & CSA, Sections R.7.9, R.7.10 and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

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