~~Confidential~~

Helsinki, 07 June 2024

Addressees
Registrants of JS_NAPHTHYLENEDIISOCYANATE as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
25 August 2015

Registered substance subject to this decision ("the Substance")
Substance name: 1,5-naphthylene diisocyanate
EC/List number: 221-641-4

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 in requests 1, 2, 5, 8 and 9 below by ***14 December 2026*** and all other requests by ***14 March 2029***.

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

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

1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202) – test on an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives.

2. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201) – test on an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives.

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

3. In vivo mammalian alkaline comet assay or Transgenic rodent somatic and germ cell gene mutation assays also requested below (triggered by Annex VIII, Section 8.4., column 2).

4. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study requested below (Annex VIII, Section 8.7.1.)
   or, in case no Extended one-generation reproductive toxicity study is requested in the adopted decision, a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats.

5. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203) – test on an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives.

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

6. Transgenic rodent somatic and germ cell gene mutation assay (triggered by Annex IX, Section 8.4.4; test method: OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach; germ cells and duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.
   OR
   In vivo mammalian alkaline comet assay (triggered by Annex IX, Section 8.4.4; test method: OECD TG 489) in rats, or if justified, in other rodent species, oral route, on the following tissues: liver, glandular stomach and duodenum.

7. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit).

8. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211) – test on an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives.

9. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210) – test on an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives.

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

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

11. 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 in request 11, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
    - Cohort 1A and 1B (Reproductive toxicity).

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

The reasons for the request(s) 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.

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.

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 request(s)
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 In your comments to the draft decision and in your updated registration dossier (20 November 2023) you have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX/X, Section 8.7.2.)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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).

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance*(s)*:

- 4,4-methylenediphenyl diisocyanate (4,4-MDI); EC 202-966-0;
- m-tolyidene diisocyanate (TDI) (EC 247-722-4).

7 You provide the following reasoning for the prediction of toxicological properties: "*A read across to the source substance 4,4'-Methylenediphenyl diisocyanate (4,4'-MDI) is warranted as the toxicity of both substances is driven by the NCO functional group*.".

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 You have provided a read-across justification document and included this document in your updated registration dossier.

10 You argue that the inhalation route is the only human relevant route of exposure based on the claim that there is no exposure to populations other than workers in an industrial environment. You further argue that oral testing would investigate substances other than the Substance, namely hydrolysis products and/or metabolites, which would not occur in inhalation and are not relevant to investigate the mutagenicity of the Substance via the inhalation route.

0.1.1. Inappropriate route of administration

11 When a grouping and read-across approach is used, the results must be adequate for the purpose of classification and labelling and risk assessment and have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.

0.1.1.1. Route of administration for in vivo mammalian somatic cell genotoxicity study

12 Regarding the information requirement for an *in vivo* mammalian somatic cell genotoxicity study, in this case in vivo mammalian alkaline comet assay or transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488 or OECD TG 489), the following specifications must be met:

(a) Unless justified, the route of exposure is the anticipated route of human exposure and it ensures adequate exposure of the target tissues (OECD TG 488, para. 41 and OECD TG 489, para. 39)

In the case of inhalation, the target tissues are at least lung, as primary site of contact, and liver (OECD TG 488, para. 54-55 and OECD TG 489, para. 42).

13 Furthermore, the same principle applies to the specifications of the study design including the route of administration. When there is flexibility, the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment. To this end, testing shall be performed at appropriately high dose levels. If dose (concentration) selection is limited by the physicochemical properties or biological effects of the test substance, justification shall be provided. (Annex IX, introductory paragraph 6).

14 You predict the properties of the Substance from the following study: *in vivo* mammalian alkaline comet assay (OECD TG 489) with the source substance MDI via the inhalation route up to concentrations of 11 mg/m^3. Tissues investigated are lung (bronchoalveolar lavage), liver and forestomach. The study outcome is "not genotoxic".

15 You have not addressed the condition of "*adequate exposure of target tissues"*, which, in the case of tissue(s) other than the lung, firstly requires that systemic exposure occurs, and secondly, that systemic concentrations are adequate for hazard identification.

16 The source substance is classified as respiratory sensitiser and as irritant, which indicates dose-limiting local effects via the inhalation route such as irritation and sensitisation. Thereby the inhalation route decreases systemic availability of the tested substance and/or metabolites that are relevant for hazard identification.

17 For the sake of completeness, as an example, publicly available information from a close analogue *m*-Tolylidene diisocyanate (2,4-TDI + 2,6-TDI) (EC 247-722-4) in ECHA's public database indicates that the choice of top-dose in a chronic/carcinogenicity study (OECD TG 453) via the oral route reached approximately 1/5 of the limit dose of a sub-chronic toxicity study (OECD TG 408). In contrast, the top concentration in a study of comparable design with the same substance *via the inhalation route* was limited to 1/5000 of the limit dose of a sub-chronic toxicity study (OECD TG 413) due to dose-limiting local toxicity. The MDI inhalation studies included in your dossier suggest the same, considering the low top dose level, 11 mg/m^3 in the Comet study and 9 mg/m^3 in the PNDT study. In the two-generation study with TDI, the top dose was 0.3 ppm. You have not provided data to demonstrate that that such low doses would ensure adequate tissue exposure.

18 On your argument that the hazard posed from a metabolite that may be formed during exposure to the Substance, ECHA considers that this contributes to the hazard profile of the Substance. This is particularly relevant for the endpoint "mutagenicity", when the suspected mechanism of carcinogenesis is genotoxic instead of non-genotoxic, which is the case for the Substance and its metabolites. You have not justified in particular that the hydrolysis product/metabolite could only form in the stomach and not in other tissues when in contact with biological fluids.

19 This indicates that the local effects via the inhalation route limit the top dose/concentration by a factor of a thousand. Therefore, the argument that the inhalation route is more suitable at identifying systemic hazards from diisocyanates is contradicted because dose-limiting

effects may occur one-thousandfold earlier than via the oral route. Therefore, you have not demonstrated that the inhalation would ensure adequate exposure of target tissues, nor that it would ensure appropriately high dose levels. This is not in line with the OECD TG and also not with the introductory paragraph to Annexes VIII-X to REACH: "*the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment. To this end, testing shall be performed at appropriately high dose levels.*" Furthermore, the formation of (bio)transformation products contributes to the hazard profile of the Substance.

20 The adaptations that rely on studies conducted via the inhalation route are not suitable to identify the hazards as explained above.

21 Therefore, your predictions may underestimate the hazards of the Substance, the results are not adequate for the purpose of classification and labelling and risk assessment and you have not demonstrated that the key parameters of the test guidelines are adequately and reliably covered.

0.1.1.2. Route of administration for reproductive toxicity studies

22 Regarding the information requirements for reproductive toxicity studies, when a substance is a liquid or solid, the study must be conducted with oral exposure of the Substance (Annex VIII, IX and X, Section 8.7.2., Column 1). Deviations may be made if scientifically justified, for example through evidence of equivalent or higher systemic exposure via another relevant route of human exposure or route-specific toxicity.

23 Your position is rejected for similar reasons as in section 0.1.1.1.

0.1.1.3. Conclusion on route of administration

24 You have not provided any justification that, after inhalation exposure, systemic availability would be sufficient. You have shown even less that equivalent or higher systemic exposure could be achieved as compared with the oral administration. In this respect, ECHA further refers to the introductory paragraph of Annexes VIII-X: in case of flexibility, "*the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment. To this end, testing shall be performed at appropriately high dose levels*".

0.1.2. Conclusion on read-across

25 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

Reasons related to the information under Annex VII of REACH

1. Short-term toxicity testing on aquatic invertebrates

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

1.1. Information provided

27 You have provided:

(i) a short-term toxicity study on Daphnia magna (2005) with the Substance;

(ii) a short-term toxicity study on Daphnia magna (1989) with the Substance.

1.2. Assessment of the information provided

1.2.1. The provided studies do not meet the specifications of the test guideline(s)

28 To fulfil the information requirement, a study must comply with OECD TG 202 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) the test duration is 48 hours or longer;

Characterisation of exposure

b) 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;

c) the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also Guidance on IRs and CSA, Section R.7.8.4.1).

29 In study (i):

Characterisation of exposure

b) The total organic carbon (TOC) in the test media was measured. The limit of detection of that method is reported to be 5 mg_{TOC}/L. The concentration of the Substance or its hydrolysis products was not measured;

c) the reported effect values are based on nominal concentrations. However, the TOC concentration in the test medium at the start and the end of the test was below the limit of detection (i.e. < 5 mg_{TOC}/L, corresponding to <7.3 mg/L of the Substance) which is not within ± 20 % of the nominal initial concentration (i.e. 100 mg/L of the Substance).

30 In study (ii):

Technical specifications impacting the sensitivity/reliability of the test

a) the test duration was 24 hours;

Characterisation of exposure

b) no analytical monitoring of exposure was conducted.

31 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results.

32 The analytical method (TOC measurement) used for study (i) is not specific to the Substance or to its hydrolysis products. The concentrations of the Substance or of its hydrolysis products in the test medium are not known.

33 That analytical method has a high limit of detection. No TOC was detected (up to the limit of detection of 5 mg_{TOC}/L) in the test media. You have not demonstrated that any test material, the Substance or its hydrolysis products, was present in the test medium.

34 Still, you have reported the effect values for study (i) based on nominal concentrations whereas, the concentration of the Substance or the corresponding concentrations of its hydrolysis products are clearly not within ± 20 % of the nominal initial concentration.

35 This may result in an underestimation of the hazard.

36 Study (ii) is not valid as its duration was limited to 24 hours and no analytical measurements of the test concentrations were performed.

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

38 Therefore, the information requirement is not fulfilled.

39 In your comments to the draft decision, you propose to perform the long-term toxicity to aquatic invertebrates study (OECD TG 211) under request 8 instead of a short-term toxicity study. Annex VII, Section 9.1.1, Column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available. At present no long-term toxicity study on aquatic invertebrates is provided in your registration dossier, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

1.3. Study design

40 The Substance is difficult to test due to its hydrolysable properties (see below). OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented.

41 First, OECD GD 23, section 7.3 recommends that "if the test chemical is likely to be unstable, a decision to test the parent test chemical and/or its degradation products, if identified, should be based on a consideration of its half-life under test and real-world conditions". The hydrolysis half-life of the Substance is less than 1 hour at pH values between 7 and 9. Therefore, the Substance is unstable in water.

42 Second, OECD GD 23, section 7.3 indicates that "testing of degradation products will normally be required where the results of a preliminary range-finding experiment or a (Q)SAR analysis indicates that the degradants have significant toxicities or other relevant properties (e.g. low or no degradability)." The available ready biodegradability studies, which are equivalent or more relevant than a preliminary range-finding experiment, show no mineralisation of the Substance which indicates the potential for building-up of hydrolysis products with low or no biodegradability.

43 Third, OECD GD 23, section 7.3, point 86 specifies that: "The aquatic toxicity of degradation products may be determined by allowing the parent compound to degrade and then exposing the test organisms to the resulting test solution. Leaving a stock or test solution of the parent test chemical for a period equal to 6 degradation half-lives of the test chemical will generally be sufficient to ensure that the test solution contains only degradation products. The pH of the test solution after allowing for degradation should be neutralised

to that of the control test medium prior to testing". Therefore, an aqueous solution of the Substance aged for a period equal to at least 6 degradation half-lives must be tested.

44 Finally, OECD GD 23, section 7.3, point 96 indicates that: "Flow-through exposure systems are not considered appropriate for chemicals which hydrolyse at high concentrations to form polymers (e.g. alkyloxysiloxanes and isocyanates) because of the potential for fouling of the test organisms and apparatus". OECD GD 23, section 7.3, point 97 further specifies that test solutions of hydrolysis products of test chemicals which polymerise should be prepared by adding the test chemical very slowly to a vessel which is part-filled with test media and being stirred rapidly so as to avoid locally high concentrations of polymerisable material. Once the test chemical has been added, the vessel should be topped up with test media to the required volume and stirred continuously for a period sufficient to ensure complete hydrolysis. This procedure should enable a test solution of the hydrolysis products to be produced without the formation of polymers". The Substance is an isocyanate and thus hydrolyses to potentially form polymers at high concentrations. Therefore, testing must comply with OECD GD 23, section 7.3, point 97.

45 In accordance with OECD GD 23, section 7.3, point 88, you must monitor the test concentration(s) of the hydrolysis products in the aged solution throughout the exposure duration, using an appropriate analytical method. You must express the effect concentration based on the measured values of the dissolved hydrolysis products.

2. Growth inhibition study aquatic plants

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

2.1. Information provided

47 You have provided a growth inhibition study on algae with the Substance.

2.2. Assessment of the information provided

2.2.1. The provided study does not meet the specifications of the test guideline(s)

48 To fulfil the information requirement, a study must comply with OECD TG 201 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

a) exponential growth in the control cultures is observed over the entire duration of the test;

b) at least 16-fold increase in biomass is observed in the control cultures by the end of the test;

c) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;

d) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Desmodesmus subspicatus*];

Technical specifications impacting the sensitivity/reliability of the test

e) three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;

f) one of the two alternative growth medium (*i.e.* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified.

49 In the provided study:

Validity criteria

a) There is no information reported to verify whether exponential growth in the control cultures was maintained over the entire duration of the test;

b) the biomass at the start and end of the test is not reported;

c) the mean coefficient of variation for section-by-section specific growth in the control is not reported and there is no information reported to calculate it;

d) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is not reported and there is no information reported to calculate it;

Technical specifications impacting the sensitivity/reliability of the test

e) the number of replicates is not reported;

f) the composition of the test medium is not described.

50 Based on the above, the information reported in the robust study summary is insufficient to verify that the validity criteria of OECD TG 201 are met and to assess the quality of the study.

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

52 In your comments, you indicate that you will provide the information necessary to verify the validity criteria and the technical specifications of the test in an updated registration dossier. At present, this information is not in your registration dossier, therefore no conclusion on the compliance can currently be made.

53 Therefore, the information requirement is not fulfilled.

2.3. Study design

54 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in ‘Study design’ under request 1.

Reasons related to the information under Annex VIII of REACH

3. In vivo mammalian alkaline comet assay or Transgenic rodent somatic and germ cell gene mutation assays

55 Under Annex VII, Section 8.4., Column 2, an appropriate *in vivo* mammalian somatic cell genotoxicity study as referred to in Annex IX, point 8.4.4, must be performed in case of a positive result in any of the *in vitro* studies referred to in Annex VIII, Section 8.4. The *in vivo* study must address the concerns raised by the *in vitro* study results, i.e. the chromosomal aberration concern or the gene mutation concern or both, as appropriate.

3.1. Triggering of the information requirement

56 Your dossier contains positive results for the *in vitro* gene mutation study in mammalian cells; however, no adequate information from an appropriate *in vivo* somatic cell genotoxicity study, according to the requirements of Annex VIII, is available.

57 Therefore, the information requirement is triggered.

3.2. Information requirement not fulfilled

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

4. Justification for an adaptation of a Screening for reproductive/ developmental toxicity based on the results of the Extended one-generation reproductive toxicity study

59 A screening study for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

4.1. Information provided

60 ECHA understands that in your updated registration dossier (20 November 2023) you have adapted this information requirement by using a grouping and read-across approach under Annex XI, Section 1.5. To support your adaptation you provided the following study:

(i) two-generation reproduction toxicity study (OECD TG 416, 1989) with the source substance m-tolyidene diisocyanate (TDI) (EC 247-722-4), conducted via inhalation.

61 In addition, you indicate your intention to use read-across to a not yet conducted extended one-generation study with the source substance 4,4'-methylenediphenyl diisocyanate (MDI; EC 202-966-0).

4.2. Assessment of the information provided

62 As explained in section 0.1., your read-across adaptation is rejected.

63 Regarding the planned study with MDI, at present the study is not available in the registration dossier and no conclusion on the compliance can currently be made.

64 Therefore, the information requirement is not fulfilled.

4.3. Study design

4.3.1. Experimental study design

65 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

66 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1). Deviations may be made if scientifically justified, for example through evidence of equivalent or higher systemic exposure via another relevant route of human exposure or route-specific toxicity.

67 In your comments to the draft decision, you argue that the oral route is not appropriate for toxicity studies of the Substance and you suggest to conduct a study via inhalation. You claim that by oral exposure, the toxicological response will be incorrectly interpreted to represent the Substance's intrinsic hazardous properties which essentially reflects the properties of the Substance which is formed as a hydrolysis product of the Substance in the stomach. Furthermore, you claim that the primary toxic effects of the Substance are focused on the port of entry, the respiratory tract. Inhalation toxicity studies with the Substance are therefore sufficient and appropriate to assess human hazard and risk.

68 First, the Substance is classified as respiratory sensitiser and as irritant, which indicates dose-limiting local effects via the inhalation route such as irritation and sensitisation. Thereby the inhalation route decreases systemic availability of the Substance and/or metabolites that are relevant for hazard identification of the Substance while you have not provided any argument that such systemic availability would still be sufficient. Even less you have demonstrated that equivalent or higher systemic exposure could be achieved. In this respect, ECHA further refers to the introductory paragraph of Annex VIII: in case of flexibility, "*the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment. To this end, testing shall be performed at appropriately high dose levels*".

69 Second, on your argument that the hazard posed from a primary reaction product (metabolite) that may be formed during oral exposure to the Substance, ECHA considers that this contributes to the hazard profile of the Substance. You have not justified in particular that the reaction product/metabolite could only form in the stomach and not in other tissues when in contact with biological fluids.

70 Therefore, you have not demonstrated that the oral route is irrelevant for assessing the human health hazards via the relevant route(s) of exposure.

71 Third, you refer to risk considerations, namely Section 0.3, of Annex I to REACH, and ECHA Guidance Chapter R.14 on exposure. However, the objective of Annex VIII is to investigate the intrinsic properties of a substance and the outcome is not meant only for risk assessment but also for hazard assessment.

72 Fourth, you refer to animal welfare considerations, but these considerations do not address the issues identified above.

73 The information provided in your comments does not change the assessment.

74 Therefore, the study must be conducted in rats with oral administration of the Substance.

4.3.2. Justification for an adaptation of the screening study

75 The present decision requests the registrants concerned to generate and submit a reliable EOGRT study (see request 11). According to Annex VIII, Section 8.7.1., Column 2, and to prevent unnecessary animal testing, a screening study for reproductive/developmental toxicity does not need to be conducted.

76 Therefore, to comply with the information requirement under Annex VIII, Section 8.7.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.7.1., Column 2.

77 In case the adopted decision no longer contains a request for a EOGRT study, you are required to provide a screening study for reproductive/developmental toxicity.

78 Therefore, you are requested to either submit:

a) a justification for adaptation according to Annex VIII, Section 8.7.1., Column 2, based on request 11; or
b) a screening study for reproductive/developmental toxicity as per the study design described in section 4.3. in case the EOGRT study is not requested in the adopted decision.

5. Short-term toxicity testing on fish

79 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

5.1. Information provided

80 You have provided a short-term toxicity study on fish with the Substance.

5.2. Assessment of the information provided

5.2.1. The provided study does not meet the specifications of the test guideline(s)

81 To fulfil the information requirement, a study must comply with OECD TG 203 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). 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;
b) in static tests, if the concentrations of the test material are not expected to remain within ± 20 % of the nominal, then the test substance concentration is determined (in one replicate) in all concentrations at the beginning, at 48 hours and at the end of the test;
c) the determinations of exposure concentrations reflect the concentrations of the dissolved chemical;

82 In the provided stuy:

Characterisation of exposure

a) The total organic carbon (TOC) in the test media was measured. The limit of detection of that method is reported to be 5 mg_{TOC}/L. The concentration of the Substance or its hydrolysis products was not measured;
b) the test was conducted under static conditions. The measured TOC concentration in the test medium at the start of the test and during the whole experiment was below the limit of detection (i.e. < 5 mg_{TOC}/L, corresponding to <7.3 mg/L of the Substance), i.e. did not remain within ± 20 % of nominal;
c) TOC measurements were conducted after filtration (pore size 7-12 µm).

83 Based on the above, there are critical methodological deficiencies that may result in an underestimation of hazard and thus resulting in the rejection of the study results.

84 The analytical method (TOC measurement) is not specific to the Substance or to its hydrolysis products. The concentrations of the Substance or of its hydrolysis products in the test medium are not known.

85 That analytical method has a high limit of detection. No TOC was detected (up to the limit of detection of 5 mg_{TOC}/L) in the test media. You have not demonstrated that any test material, the Substance or its hydrolysis products, was present in the test medium.

86 Still, you have reported the effect values based on nominal concentrations, whereas the concentrations of the Substance or the corresponding concentrations of its hydrolysis products are clearly not within ± 20 % of the nominal initial concentrations.

87 You explain that TOC measurements were conducted after filtration (pore size 7-12 µm) without justification to demonstrate that such filtration allowed the determination of exposure concentrations reflecting the concentrations of the dissolved chemical. Filters with a smaller pore size (typically 0.45 µm or less e.g. 0.2 µm) are generally recommended to isolate the soluble fraction of a sample. Therefore, you have not demonstrated that your analytical method would reflect the concentrations of the dissolved Substance or of its dissolved hydrolysis products.

88 On this basis, the specifications of OECD TG 203 are not met.

89 Therefore, the information requirement is not fulfilled.

90 In your comments to the draft decision, you propose to perform the long-term toxicity to fish study (OECD TG 210) under request 9 instead of a short-term toxicity study. Annex VIII, Section 9.1.3, Column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on fish is available. At present no long-term toxicity study on fish is provided in your registration dossier, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

5.3. Study design

91 OECD TG 203 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under request 1.

Reasons related to the information under Annex IX of REACH

6. In vivo mammalian alkaline comet assay; or Transgenic rodent somatic and germ cell gene mutation assays

92 An appropriate *in vivo* mammalian somatic cell genotoxicity study is an information requirement under Annex IX, Section 8.4.4., if there is a positive result in any of the *in vitro* studies referred to in Annex VII or VIII, Section 8.4.

6.1. Triggering of the information requirement

93 Your dossier contains positive results for the *in vitro* gene mutation study in mammalian cells which raise the concern for gene mutation.

94 Therefore, an in vivo mammalian somatic cell genotoxicity study is triggered.

6.2. Information provided

95 Your dossier contains the following *in vivo* studies:

(i) in vivo mammalian somatic cell study: cytogenicity / erythrocyte micro-nucleus (OECD TG 474, 2009) with the Substance
(ii) in vivo mammalian cell study: DNA damage and/or repair (OECD TG 486, 2011) with the Substance.

96 In addition, in your comments to the initial draft decision you have adapted this information requirement by using grouping and read-across approach under Annex XI, Section 1.5. To support your adaptation you provided the following study (also included in your updated dossier):

(iii) in vivo mammalian alkaline Comet assay (OECD TG 489, 2017) with the source substance 4,4'-diphenylmethane diisocyanate (MDI) (EC 202-966-0), conducted via inhalation.

97 We have assessed this information and identified the following issue(s):

6.3. Assessment of the information provided

6.3.1. Studies (i) and (ii) not adequate for the information requirement

98 (Eco)toxicological studies must comply with a recognised test method (Article 13(3) of REACH). To address the specific concern raised by the *in vitro* positive result, an *in vivo* somatic cell genotoxicity study must be conducted according to the OECD TG 488 or 489, Guidance on IRs and CSA, Section R.7.7.6.3. Such study must cover the key parameters of the corresponding OECD test guideline (Article 13(3) of REACH).

99 The study (i) is described as an in vivo erythrocyte micronucleus test. This study is not an *in vivo* somatic cell genotoxicity study addressing concerns for gene mutations.

100 The study (ii) is described as a UDS test. This is an indicator test that detects some DNA repair mechanisms (measured as unscheduled DNA synthesis in liver cells). However, as reminded in the Guidance on IRs & CSA, R.7a, Section R.7.7.6.3 (page 571-572), the UDS test is sensitive to some (but not all) DNA repair mechanisms and not all gene mutagens are positive in the UDS test. The sensitivity of the UDS test has been questioned (Kirkland and Speit, 2008 [1]) and its lower predictive value towards rodent carcinogens and/or in vivo genotoxicants has been confirmed in comparison with the TGR assay and comet assay (EFSA, 2017 [2]). Therefore, a negative result in a UDS assay alone is not a proof that a substance does not induce gene mutation. Moreover, though a positive result in the UDS

assay can indicate exposure of the liver DNA and induction of DNA damage by the substance under investigation, it is not sufficient information to conclude on the induction of gene mutation by the substance.

[1] Kirkland D and Speit G (2008) Evaluation of the ability of a battery of three *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens III. Appropriate follow-up testing *in vivo*. Mutat Res 654:114-32.

[2] EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger M, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Younes M, Aquilina G, Crebelli R, Gurtler R, Hirsch-Ernst KI, Mosesso P, Nielsen E, van Benthem J, Carfì M, Georgiadis N, Maurici D, Parra Morte J and Schlatter J, 2017. Scientific Opinion on the clarification of some aspects related to genotoxicity assessment. EFSA Journal 2017;15(12):5113, 25 pp. https://doi.org/10.2903/j.efsa.2017.5113.

101 Based on the above, the studies (i) and (ii) are not adequate for the information requirement.

6.3.2. Your read-across adaptation

102 As explained in section 0.1., your read-across adaptation is rejected.

103 Therefore, the information requirement is not fulfilled.

104 ECHA considers that an appropriate *in vivo* follow up genetic toxicity study is necessary to address the concern identified *in vitro*.

6.4. Test selection

105 According to the Guidance on IRs & CSA, Section R.7.7.6.3 either the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) or the transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) are suitable to follow up a positive *in vitro* result on gene mutation.

6.4.1. Specification of the study design

6.4.1.1. Comet assay

106 In case you decide to perform the comet assay, according to the test method OECD TG 489, rats are the preferred species. Other rodent species can be used if scientifically justified (OECD TG 489, paragraph 23).

107 Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

108 In your comments to the draft decision, you have argued that testing should be conducted via inhalation for the reasons described in relation to your read-across adaptation (section 0.1.) which must be rejected for the same reasons.

109 In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

6.4.1.1.1. Cross-linking properties

110 You are reminded that you may decide to take into account the potential cross-linking properties of the Substance in the experimental setup of the comet assay and perform a modified comet assay in order to detect cross links. Therefore, you may consider preparing and analysing two sets of slides: one set of slides submitted to the standard experimental conditions (as described in the OECD TG 489); the other set of slides submitted to modified experimental conditions that enable the detection of DNA crosslinks. The modified experimental conditions may utilise one of the following options: (1) increase of electrophoresis time, e.g. as described in reference 23 *[1]* in the OECD TG 489; (2) treatment of isolated cells (either in suspension or embedded in the slides) with a chemical (e.g. MMS); or (3) treatment of isolated cells (either in suspension or embedded in the slides) with ionising radiation (options 2 and 3 are described e.g. in references 36-39 *[2-5]* in the OECD TG 489 or Pant et al. 2015 *[6]*). In order to ensure the robustness of the test result a specific positive control group of animals would be needed.

[1] Nesslany *et al.* (2007) *In vivo* comet assay on isolated kidney cells to distinguish genotoxic carcinogens from epigenetic carcinogens or cytotoxic compounds *Muta Res*;630(1-2):28-41.

[2] Merk and Speit (1999) Detection of crosslinks with the comet assay in relationship to genotoxicity and cytotoxicity. *Environ Mol Mutagen*;33(2):167-72.

[3] Pfuhler and Wolf (1996) Detection of DNA-crosslinking agents with the alkaline comet assay. *Environ Mol Mutagen*;27(3):196-201.

[4] Wu and Jones (2012) Assessment of DNA interstrand crosslinks using the modified alkaline comet assay. *Methods Mol Biol*;817:165-81.

[5] Spanswick *et al.* (2010) Measurement of DNA interstrand crosslinking in individual cells using the Single Cell Gel Electrophoresis (Comet) assay. *Methods Mol Biol*;613:267-282.

[6] Pant K *et al.* (2015) Modified *in vivo* comet assay detects the genotoxic potential of 14-hydroxycodeinone, an α,β -unsaturated ketone in oxycodone. *Environ Mol Mutagen*;56(9):777-87.

6.4.1.2. TGR assay

111 In case you decide to perform the TGR assay, according to the test method OECD TG 488, the test must be performed in transgenic mice or rats.

112 Also, according to the test method OECD TG 488, the test substance is usually administered orally.

113 In your comments to the draft decision, you have argued that testing should be conducted via inhalation for the reasons described in relation to your read-across adaptation (section 0.1.) which must be rejected for the same reasons.Based on OECD TG 488, you are requested to follow the 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals.

114 According to the test method OECD TG 488, the test must be performed by analysing tissues from liver, as slowly proliferating tissue and primary site of xenobiotic metabolism, and from glandular stomach and duodenum, as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 ºC) until the analysis of liver

and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

6.4.1.3. Germ cells

115 In case you choose to perform a comet assay, you may consider collecting the male gonadal cells from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

116 In case you choose to perform a TGR assay, you must collect the male germ cells (from the seminiferous tubules) at the same time as the other tissues, to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). This duration is sufficient to allow you or ECHA to decide on the need for assessment of mutation frequency in the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

7. Pre-natal developmental toxicity study in one species

117 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

7.1. Information provided

118 In your updated registration dossier (20 November 2023) and in your comments to the initial draft decision you have adapted this information requirement by using a grouping and read-across approach under Annex XI, Section 1.5. To support your adaptation you provided the following study:

(i) PNDT study (OECD TG 414, 1996) with the source substance 4,4'-diphenylmethane diisocyanate (MDI) (EC 202-966-0), conducted via inhalation.

7.2. Assessment of the information provided

119 As explained in section 0.1., your read-across adaptation is rejected.

120 Therefore, the information requirement is not fulfilled.

7.3. Study design

121 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

122 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

123 In your comments to the draft decision, you have argued that testing should be conducted via inhalation for the reasons described in relation to your read-across adaptation (section 0.1.) which must be rejected for the same reasons.Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

8. Long-term toxicity testing on aquatic invertebrates

124 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

8.1. Information provided

125 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification:

126 "In accordance with column 2 of REACH Annex IX, long-term toxicity studies with invertebrates do not need to be conducted as from the chemical safety assessment it can be concluded that there is no risk for aquatic organisms based on short-term toxicity data".

8.2. Assessment of the information provided

8.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

127 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to aquatic invertebrates referred to under Column 1, Section 9.1.5.

128 Therefore, your adaptation is rejected and the information requirement is not fulfilled.

129 In your comments to the draft decision, you agree to perform the requested study.

8.3. Study design

130 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under request 1

9. Long-term toxicity testing on fish

131 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

9.1. Information provided

132 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification:

133 "In accordance with column 2 of REACH Annex IX, long-term toxicity studies with fish do not need to be conducted as from the chemical safety assessment it can be concluded that there is no risk for aquatic organisms based on short-term toxicity".

9.2. Assessment of the information provided

9.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

134 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

135 Therefore, your adaptation is rejected and the information requirement is not fulfilled.

136 In your comments to the draft decision, you agree to perform the requested study.

9.3. Study design

137 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

138 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under request 1.

Reasons related to the information under Annex X of REACH

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

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

10.1. Information provided

140 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following information provided in your updated dossier (20 November 2023) and with your comments on the initial draft decision:

(i) PNDT study (OECD TG 414, 1996) in rats with the source substance 4,4'-diphenylmethane diisocyanate (MDI) (EC 202-966-0).
(ii) two-generation reproduction toxicity study (OECD TG 416, 1989) in rats with the source substance m-tolyidene diisocyanate (TDI) (EC 247-722-4).
(iii) sub-chronic (90-days) study (OECD TG 413, 2010) in rats with the Substance
(iv) acute toxicity study (OECD TG 403, 2004) in rats with the Substance
(v) sub-acute (5-days) study (1975) in rats with the Substance
(vi) sub-acute (5-days) study (1975) in mice with the Substance
(vii) sub-acute (5-days) study (1975) in guinea pigs with the Substance;
all (studies i-vii) conducted via inhalation.

141 In addition, you provided:

(viii) human biomonitoring study (2003)

142 Furthermore, you refer to data presenting the reactivity pattern and respiratory irritation caused by different isocyanates.

10.2. Assessment of the information provided

143 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.

144 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.

145 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.

10.2.1. Assessment of relevant information

146 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) prenatal developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

147 Study (i) provides relevant information that covers 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy in rat. Study (ii) covers 2) maternal toxicity and 3) maintenance of pregnancy in rat.

148 The studies (iii-viii) were conducted with different species, but do not provide relevant information to support your adaptation as they were not investigating pregnant animals/humans and do not cover the aspects 1-3) listed above.

149 Therefore, you have only provided relevant information on one species.

150 In your comments you bring general arguments about lack of systemic effects after inhalation exposure and you hypothesise that there would not be any differences between species. You have not provided data or assessed the key parameters 1-3) listed above and therefore these arguments are not relevant. In addition, your arguments focus on local effects observed after inhalation exposure, whereas the information requested is via oral administration (see section 10.3.).

151 Based on the above, your adaptation is rejected.

152 Therefore, the information requirement is not fulfilled.

10.3. Study design

153 A PNDT study according to the test method OECD TG 414 should be performed in rabbit or rat as preferred second species, depending on the species tested in the first PNDT study (request 7 in this decision).

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

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

11. Extended one-generation reproductive toxicity study

156 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.

11.1. Information provided

157 In your updated registration dossier (20 November 2023) and in your comments to the initial draft decision you have adapted this information requirement by using grouping and read-across approach under Annex XI, Section 1.5. To support your adaptation you provided the following study:

(i) two-generation reproduction toxicity study (OECD TG 416, 1989) with the source substance m-tolyidene diisocyanate (TDI) (EC 247-722-4) conducted via inhalation.

158 In addition, you indicate your intention to use read-across to a not yet conducted EOGRT study with the source substance 4,4'-methylenediphenyl diisocyanate (MDI; EC 202-966-0).

11.2. Assessment of the information provided

159 As explained in section 0.1., your read-across adaptation is rejected.

160 Therefore, the information requirement is not fulfilled.

11.3. Study design

11.3.1. Species and route selection

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

162 In your comments to the draft decision, you have argued that testing should be conducted via inhalation for the reasons described in relation to your read-across adaptation (section 0.1.) which must be rejected for the same reasons.

11.3.2. Pre-mating exposure duration

163 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.

164 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.).

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

11.3.3. Dose-level setting

166 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; introductory part of Annex IX/X to REACH; Annex I, Section 1.0.1. to 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.

167 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.

168 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.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.

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

170 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.

11.3.4. Cohorts 1A and 1B

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

11.3.4.1. Histopathological investigations in Cohorts 1A and 1B

172 In addition to histopathological investigations of cohorts 1A, 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, paragraph 67 and 72) if

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

11.3.4.2. Splenic lymphocyte subpopulation analysis

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

11.3.4.3. Investigations of sexual maturation

174 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.

11.3.5. Further expansion of the study design

175 The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 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 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

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 16 November 2022.

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).

The deadlines of the decision are set based on standard practice for carrying out OECD TG tests. They have been exceptionally extended by 12 months from the standard deadlines granted by ECHA to take into account currently longer lead times in contract research organisations.

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]
[redacted]	[redacted]	[redacted]
[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 (https://echa.europa.eu/practical-guides).

(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.
- The reported composition must include all constituents of each Test Material and their concentration values.

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).