~~Confidential~~

Helsinki, 11 August 2022

Addressees
Registrant(s) of JS_126-30-7_Neopentylglycol as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
29/03/2017

Registered substance subject to this decision ("the Substance")
Substance name: 2,2-dimethylpropane-1,3-diol
EC number: 204-781-0

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 information under request 1 below by ***18 November 2024*** and all other information listed below by ***19 May 2026***.

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

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

1. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

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

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

3. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, 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); and
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

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

The reasons for the decision(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 decision
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 decision

Contents

Reasons related to the information under Annex IX of REACH

1. Long-term toxicity testing on fish

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

1.1. Information provided

2 You have provided the following justification to omit the study: "One long-term study on aquatic invertebrates is already available. Furthermore, fish are not the most sensitive species. Therefore, and because of reasons of animal welfare, no long-term study on fish is proposed".

1.2. Assessment of the information provided

3 We have assessed this information and identified the following issue:

4 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

5 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

6 Therefore, you have not demonstrated that this information can be omitted. Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

7 On this basis, your adaptation is rejected.

1.3. Information provided in your comments

8 In your comments to the draft decision, you propose to adapt the information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) according to Annex XI, section 1.3 of REACH.

9 You have derived a 28-d NOEC for mortality of fish using a trend analysis developed with the OECD QSAR Toolbox v4.5.

10 In addition, you have used several profilers included in the OECD QSAR Toolbox to conclude that the Substance is not expected to cause critical long-term effects to aquatic organisms.

11 Annex XI, Section 1.3. specifies that the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the predictions need to be derived from scientifically valid models,
2. the substance must fall within the applicability domain of the models,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

12 With regard to these conditions, we have identified the following issues:

1.3.1. The endpoint predicted by the (Q)SAR model is insufficient to cover the information requirement

13 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint, the training set must be obtained from experimental data generated with homogeneous experimental protocols, and the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement. For the present information requirement, OECD test guideline 210 is the preferred experimental protocol to be followed. The effects measured by that test guideline include parameters related to the survival and development of fish in early life stages from the stage of fertilised eggs until the juvenile life-stage:

i. the stage of embryonic development at the start of the test, and
ii. hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
iii. the appearance and behaviour of larvae and juvenile fish, and
iv. the weight and length of fish at the end of the test

14 You have not indicated with what experimental protocol(s) the data used for obtaining your training set have been generated. Therefore, it is not clear and it cannot be excluded that the training set was obtained based on heterogeneous protocols.

15 Furthemore, it cannot be established that the endpoint predicted by your model is equivalent to the endpoints measured by OECD 210. You specify that the effect predicted by your model is "mortality of fish". However, you do not specify whether the mortality is for embryos, larvae, juvenile or adult fish.

16 Finally, you have not modelled other parameters measured in OECD TG 210, in particular quantitative ones like effects on the weight and length of fish.

17 Therefore the endpoint predicted by your model is not well defined and is insufficient to cover the observations measured by OECD test guideline 210. Therefore, you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

1.3.2. Inadequate documentation of the model (QMRF)

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

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

19 In your comments to the draft decision and the associated documentation you have provided as attached files[2], you indicate that a total of 22 data points from the following chemicals were used to constitute the training set of your model: 1,1,2 Trichloroethane, Anethole, Dichloromethane, 3,4-Dichlorotoluene, 4-Butoxy-2,3-difluor-4'-methyl-1,1'-biphenyl, Dibromomethane, 4-Ethoxy-2,3-difluor-4'-propyl-1,1'-biphenyl, 1,1,2,2-Tetrachloroethane, Diuron.

[2] [redacted]

20 However, you have not provided the data, the information on the experimental protocol used to generate those data, or the data quality for the dataset used to develop the model. In the absence of such documentation, ECHA cannot trace the source and verify the quality of the individual data points. As such, the information provided is insufficient for ECHA to assess the quality and reliability of those data and how they could support the prediction.

1.3.3. The prediction is not adequate due to low reliability

21 Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest,
- reliable input parameters are used,
- the prediction must be reliable based on the representativeness (and homogeneity) of the elements in the training set.

22 You use the following chemicals as a training set for your model: 1,1,2 Trichloroethane, Anethole, Dichloromethane, 3,4-Dichlorotoluene, 4-Butoxy-2,3-difluor-4'-methyl-1,1'-biphenyl, Dibromomethane, 4-Ethoxy-2,3-difluor-4'-propyl-1,1'-biphenyl, 1,1,2,2-Tetrachloroethane, Diuron.

23 Your Substance (Neopentylglycol) is a branched diol. However, none of the chemicals in the training set are branched diols. They have different functional groups or different meaningful fragments, different physico-chemical, (eco)toxicity or mechanistic profiles (as it can be demonstrated using e.g. the profilers from the OECD QSAR Toolbox), and you have not demonstrated that they can be regarded as structurally similar to the Substance (e.g. the Tanimoto similarity indices are <<80%, irrespective of the fingerprint method used to encode the structures).

24 Structural similarity indices (e.g. the Tanimoto similarity index) and profilers (e.g. those included in the OECD QSAR Toolbox) show that the substances in the training set are not only very different from the Substance but also generally very different from each other. Therefore, the training set of your model cannot be regarded as homogeneous. This significantly affects its representativeness for the Substance you aim to predict. The heterogeneity of the training set increases the uncertainty on the prediction which is partly reflected by the large 95% prediction intervals reported by the OECD QSAR Toolbox: i.e. 1.5 to 3010 mg/L.

25 The information provided in your comments does not establish that the training set used for your model is representative and homogeneous. You have not established that your model predicts well substances that are similar to the Substance, and you have not established that it is applicable to your Substance with the necessary level of reliability. Therefore, you have not demonstrated that your model is scientifically valid and that the prediction from this model is adequate for the purpose of classification and labelling and/or risk assessment.

1.3.4. Profilers are as such not adequate to predict the absence of concern

26 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

27 You have used several profilers included in the OECD QSAR Toolbox to conclude that the mode of action of the Substance is narcotic and that critical long-term effects on aquatic organisms are not to be expected.

28 Profilers included in the OECD QSAR Toolbox were developed for the purpose of identifying analogues but not to make predictions. Measures of internal performance and predictivity are not available for those profilers. Therefore, profilers as such are not considered a scientifically valid approach to meet the information requirement.

1.4. Conclusion

29 Therefore, the information requirement is not fulfilled.

1.5. Study design and test specifications

30 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.).

Reasons related to the information under Annex X of REACH

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

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

2.1. Information provided

32 You have adapted this information requirement. While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Column 2 of Annex X, Section 8.7. To support the adaptation, you have provided following information:

(i) Adaptation justfication: *"The overall toxicity of 2,2-dimethylpropane-1,3-diol is supposed to be low. After oral application the substance is primarily conjugated with glucuronic acid and excreted via urine. According to the results of an OECD 422 reproductive toxicity screening study 2,2-dimethylpropane-1,3-diol is not reprotoxic up to and including the limit dose of 1000 mg/kg bw/d. Concerning developmental toxicity and teratogenicity, no test substance-related effects were observed up to 1000 mg/kg bw in the available OECD 414 ([redacted] 2013) and OECD 422 ([redacted] 1993) study."*

You further refer to animal welfare considerations to support your justification.

(ii) OECD TG 414 study with the Substance (2013), in the rat as first species;

(iii) OECD TG 422 study with the Substance (1993), in the rat;

(iv) Non-guideline toxicokinetic study with the Substance (1960), in rabbits.

2.2. Assessment of the information provided

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

34 Under Section 8.7., column 2 of Annex X to REACH, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:

- that it can be proven from toxicokinetic data that no systemic absorption occurs *via* relevant routes of exposure; and
- that there is no or no significant human exposure.

35 You indicate that study (iv) shows rapid absorption of the Substance in the rabbit after oral exposure, followed by conjugation with glucuronic acid and excretion via the urine.

36 Studies (ii) and (iii), as well as other in vivo studies available in your dossier, show systemic effects, like renal toxicity, in the rat after oral administration.

37 Your registration dossier mentions consumer uses, article service life and widespread uses by professional.

38 Study (iv) shows rapid absorption of the Substance in the rabbit after oral exposure, and studies (ii) and (iii) show systemic effects, thereby showing absorption of the Substance.

39 The uses of the Substance do not exclude significant human exposure.

40 Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

41 Therefore, your adaptation is rejected.

42 On this basis, the information requirement is not fulfilled.

2.3. Specification of the study design

43 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).

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

45 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

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

3. Extended one-generation reproductive toxicity study

47 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X to REACH (Section 8.7.3.).

3.1. Information provided

48 You have adapted this information requirement. While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Column 2 of Annex X, Section 8.7. To support the adaptation, you have provided following information:

(i) Adaptation justification: *"The overall toxicity of 2,2-dimethylpropane-1,3-diol is supposed to be low. After oral application the substance is primarily conjugated with glucuronic acid and excreted via urine. According to the results of an OECD 422 reproductive toxicity screening study 2,2-dimethylpropane-1,3-diol is not reprotoxic up to and including the limit dose of 1000 mg/kg bw/d. The indices of copulation, fertility, gestation, implantation, delivery, birth and viability of pubs were not affected. There was no hint for any impairment of fertility. Moreover, the available subchronic toxicity study according to OECD 408 ([redacted] 2013) revealed no test substance-related effects on estrous cycle lenght and the number of cycles and no effects were observed concerning the motility of the sperms and the incidence of abnormal sperms in the cauda epididymidis as well as the sperm head counts in the testis and in the cauda epididymidis up to and including the limit dose of 1000 mg/kg bw. Furthermore, no findings were observed within the histopathological examination of the sexual organs (epididymis, seminal vesicles, testis, ovaries, uterus, vagina). Concerning developmental toxicity and teratogenicity, no test substance-related effects were observed up to 1000 mg/kg bw in the available OECD 414 ([redacted] 2013) and OECD 422 ([redacted] 1993) study."*

49 You further refer to animal welfare considerations to support your justification.

(ii) OECD TG 408 study with the Substance (2013), in the rat;

(iii) OECD TG 414 study with the Substance (2013), in the rat as first species;

(iv) OECD TG 422 study with the Substance (1993), in the rat;

(v) Non-guideline toxicokinetic study with the Substance (1960), in the rabbit.

3.2. Assessment of the information provided

50 Under Section 8.7., column 2 of Annex X to REACH, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:

- that it can be proven from toxicokinetic data that no systemic absorption occurs *via* relevant routes of exposure; and
- that there is no or no significant human exposure.

51 You indicate that study (v) shows rapid absorption of the Substance in the rabbit after oral exposure, followed by conjugation with glucuronic acid and excretion via the urine.

52 Studies (ii), (iii) and (iv), as well as other in vivo studies available in your dossier, show systemic effects, like renal toxicity, in the rat after oral administration.

53 Your registration dossier mentions consumer uses, article service life and widespread uses by professional.

54 Study (v) shows rapid absorption of the Substance in the rabbit after oral exposure, and studies (ii), (iii) and (iv) show systemic effects, thereby showing absorption of the Substance.

55 The uses of the Substance do not exclude significant human exposure.

56 Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

57 Therefore, your adaptation is rejected.

58 On this basis, the information requirement is not fulfilled.

3.3. Specification of the study design

3.3.1. Species and route selection

59 A study according to the test method OECD TG 443 must be performed in rats with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

3.3.2. Pre-mating exposure duration

60 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.

61 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.).

62 In the comments to the draft decision you disagree with the request of ten weeks pre-mating exposure duration. You consider that in light of the available data, a two-week pre-mating exposure duration is sufficient. You state that a request for ten weeks is not in line with the REACH information requirement (Annex X, Section 8.7.3), OECD TG 443, OECD GD 151 or REACH Article 25, and such a request requires a scientific justification from ECHA. Finally, you consider that the ECHA Guidance documents are not legally binding and therefore they do not overrule the legal text or the test guideline requirements.

63 OECD TG 443 and GD 151 state that in most cases, a two-week premating exposure is sufficient, however it can be adapted when justified. ECHA agrees that the available data does not show impairment of spermatogenesis or effects on oestrous cycle (cf. OECD TG 443, para 28), however notes that the available OECD TG 422 and 408 studies provide limited information with regard to mating and fertility. The OECD TG 422 study has a two-week pre-mating exposure duration not covering the full spermatogenesis and folliculogenesis, whereas the exposure in the OECD TG 408 study is twelve weeks with no information on mating. In addition, the statistical power is low in these studies compared to EOGRTS.

64 ECHA highlights that the EOGRT study should fulfil regulatory requirements and be capable of providing information on fertility that is adequate for example for hazard identification and risk assessment as well as classification and labelling, including categorisation (OECD TG 443, paragraph 22). For these purposes, the ten weeks premating exposure duration is one of the elements together with the appropriate dose level selection which allow production of data for an informed decision making for classification and labelling, including categorisation, for the hazard endpoint for sexual function and fertility, and for risk assessment.

65 A ten weeks pre-mating exposure duration covers the full spermatogenesis and maturation meaning that the full cycle of development of sperm from spermatogonia into mature sperm is exposed. Thus, ten weeks premating exposure duration allows an assessment of the adverse effects on fertility by combining the information from all possible parameters in males evaluated at the same time. Similarly, the folliculogenesis is fully covered only after a long exposure period, such as ten weeks. It is important to expose all the developmental stages of the sperm and follicles before the mating in order to be able to evaluate any potential adverse effect on fertility.

66 If the premating exposure is only two weeks, this exposure duration does not cover the full cycle of gamete production and therefore possible fertility effects resulting from effects of the Substance on the whole cycle of gamete production can be missed. Therefore, such study would be considered inconclusive for such effects for classification and labelling purposes.

67 With regard to animal welfare, you consider that a longer pre-mating exposure duration would be linked to animal pain and stress without producing any additional information. As explained above, the ten weeks pre-mating exposure duration is needed to allow production of data for an informed decision making.

68 ECHA notes that, under Article 41(3) of REACH, this decision is to require any information needed to bring the registration dossier into compliance. In relation to pre-mating exposure, ECHA refers you to recital 7 of Commission Regulation 2015/282, which brings further indication of what it should mean in the context of the EOGRTS: "It should be ensured that the reproductive toxicity study carried-out under point 8.7.3 of Annexes IX and X to Regulation (EC) No 1907/2006 will allow adequate assessment of possible effects on fertility. The premating exposure duration and dose selection should be appropriate to meet risk assessment and classification and labelling purposes as required by Regulation (EC) No 1907/2006 and Regulation (EC) No 1272/2008 of the European Parliament and of the Council."

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

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

3.3.3. Dose-level setting

71 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, para. 22; OECD GD 151, para. 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.

72 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; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

73 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.

74 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) (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.

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

76 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.

3.3.4. Cohorts 1A and 1B

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

3.3.4.1. Histopathological investigations in Cohorts 1A and 1B

78 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, para. 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.

3.3.4.2. Splenic lymphocyte subpopulation analysis

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

3.3.4.3. Investigations of sexual maturation

80 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, para. 12 in conjunction with OECD TG 443, para. 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.

3.4. Further expansion of the study design

81 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 Column 2, Section 8.7.3., Annex IX/X. 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).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

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

The compliance check was initiated on 14 December 2020.

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

ECHA took into account your comments and did not amend the deadline.

In your comments to the draft decision, you requested an extension of the deadline to provide information for request 3 from 30 to 48 months from the date of adoption of the decision.

You justified the request by additional time required to complete the testing due to limited capacity of CROs. You further referred to one CRO that cannot start any OECD TG 443 study before Q1 2023. However, you did not provide any documentary evidence to justify your request.

On this basis, ECHA has not modified the deadline to provide the information.

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.

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. This is independent of the extension of the dealine you requested in the comments to the draft decision, which at the time was not substantiated by documentary evidence, as explained above.

Appendix 3: Addressees 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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[3].

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 and other parameters relevant for the property to be tested.

This information is needed to assess 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[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals