~~Confidential~~

Helsinki, 30 May 2024

Addressee(s)
Registrant(s) of RECONSILE EC# 205-491-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
27 May 2021

Registered substance subject to this decision ("the Substance")
Substance name: decamethyltetrasiloxane
EC/List number: 205-491-7

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***6 March 2028***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.)

   a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and

   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

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

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

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

3. Extended one-generation reproductive toxicity study (Annex IX, 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 section 3.3, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;

- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

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)

Reasons common to several requests

0.1. Read-across adaptation rejected

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

- Skin sensitisation (Annex VII, Section 8.3.)
- *In vitro* micronucleus study (Annex VIII, Section 8.4.2.)

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

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

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

0.1.1. Predictions for toxicological properties

5 You provide a read-across justification document in Section 13.1 (Chemical Safety Report). You also refer to the document "[redacted]" in Section 13. However, this document does not mention the source substance (EC 203-497-4). Therefore, it was not considered during the assessment of the read-across approach for the information requirements cited above.

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

- L3, octamethyltrisiloxane (EC 203-497-4, CAS 107-51-7).

7 You provide the following reasoning for the prediction of toxicological properties:

- for skin sensation: "*Decamethyltetrasiloxane* (L4) *belongs to the structural class of siloxanes (alkyl, vinyl, aryl or hydrogen substituted). The substances all have high log Kow (increasing with increasing chain length) and low water solubility*";
- for mutagenicity: "*L3 was selected as read-across substance because it has the same hydrolysis products as L4, and both substances hydrolyse slowly (see CSR Section 4.1.1.1). Neither substance has any functional groups that are associated with genetic toxicity*".

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

0.1.1.1. Inadequate read-across hypothesis

9 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include an explanation why the properties of the Substance may be predicted from other substances in the group, i.e. a read-across hypothesis. This hypothesis should be based on recognition

of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3.).

10 Your read-across hypothesis is based on the structural similarity between the Substance and the source substance.

11 The Substance contains one more Si group compared to the analogue substance. You do not explain why the structural differences between the substances do not influence the toxicological properties or do so in a regular pattern.

12 You have not provided a well-founded hypothesis to establish a reliable prediction for the toxicological properties, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substance.

0.1.1.2. Missing supporting information to compare properties of the substances

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

14 Supporting information must include information on the impact of exposure to the parent compounds on the prediction and bridging studies to compare the properties of the substances.

15 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance causes the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the source substance is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance.

16 You provide hydrolysis half-lives to demonstrate that both the Substance and the source substance hydrolyse slowly which is indicative of exposure to the parent compounds.

17 You provide the studies on the source substance used in the prediction in the registration dossier. Apart from these studies you have not provided any other relevant data for the Substance or the source substance. In particular, your read-across justification or the registration dossier does not include any bridging studies relevant to the adapted information requirements that would confirm that the Substance and the source substance (parent compounds) cause the same type of effects.

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

0.1.1.3. Inadequate or unreliable study on the source substance

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

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

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

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

0.1.2. Conclusion

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

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

22 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

1.1. Information provided

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

(i) A Guinea Pig Maximisation Test (1999; 712888) with the source substance EC 203-497-4.

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Read-across adaptation rejected

24 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

25 On this basis, the information provided does not contribute to the assessment whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

26 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

27 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

28 Therefore, the information requirement is not fulfilled.

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

1.3. Study design

30 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

31 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

Reasons related to the information under Annex VIII of REACH

2. *In vitro* micronucleus study

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

2.1. Information provided

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

(i) an *in vitro* cytogenicity study in mammalian cells (2008; 2008-STEC-3521) with the source substance EC 203-497-4.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

34 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

2.2.1.1. Inadequate or unreliable study on the source substance

35 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473 or OECD TG 487. Therefore, the following specifications must be met:

b) the maximum concentration tested induces 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

c) at least 300 well-spread metaphases are scored per concentration;

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

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

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

36 In study (i):

a) You indicate that "*substantial cytotoxicity observed at dose levels > 23.4 ug/mL in all three treatment groups*". You did not show that the maximum tested concentration induced 55+5% of cytotoxicity compared to the negative control, or that it induced the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;

b) 200 metaphases (*i.e.*, less than 300 metaphases) were scored per concentration;

c) the historical positive control database is not reported;

d) the historical control range of the laboratory is not reported;

e) data on the cytotoxicity (cell growth inhibition) for the treated and control cultures are not reported.

37 Based on the above, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

38 Therefore, the information requirement is not fulfilled.

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

2.3. Study design

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

2.3.1. Assessment of aneugenicity potential

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

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

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

Reasons related to the information under Annex IX of REACH

3. Extended one-generation reproductive toxicity study

43 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX, Section 8.7.3., if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore Column 2 defines the conditions under which the study design needs to be expanded.

3.1. Triggering of the information requirement

44 You claim that "*the extended one-generation reproductive toxicity study does not need to be conducted because there are no results from available repeated dose toxicity studies that indicate adverse effects on reproductive organs or tissues, or reveal other concerns in relation with reproductive toxicity*".

45 However, the short-term repeated dose toxicity study on the Substance (2010, 2009-I0000-61677), the screening study for reproductive and developmental toxicity study on the Substance (2007, 2007-I0000-58160) and the pre-natal developmental toxicity on the Substance (2020, BJ12FM) in your dossier indicate adverse effects on reproductive organs and reveal other concerns in relation with reproductive toxicity.

46 Specifically:

- in the short-term repeated dose toxicity, there is evidence of changes in endocrine organ weight: "*after two weeks recovery, males had significantly elevated mean absolute and relative thyroid weights (all p<0.05) that were not evident after the treatment period*". There is also evidence of follicular hypertrophy in one male at the highest dose: "*follicular cell hypertrophy at minimal severity was recorded in a single male treated with 1000 mg/kg bw/day*";
- in the screening study for reproductive and developmental toxicity, there are indications of reduced litter size and increased incidence of abortions: "*three female rats in the 400 ppm group with evidence of copulation failed to deliver a litter. One of these three females showed signs of parturition (blood discharge) on gestation day 25, but no pups were found. However, seven implant sites were present*". The presence of implantation sites shows that foetuses were formed, however they were not delivered. In addition, the signs of parturition reported at gestation day 25 raise concern, because pups are usually born around gestation day 20;
- in the pre-natal developmental toxicity study, there is evidence of changes in the thyroid glands (increase in the incidence of diffuse follicular cell hypertrophy) and in thyroid hormone levels (increase in TSH levels and decrease in T3 and T4 levels).

47 Therefore, the information requirement is triggered.

3.2. Information requirement not fulfilled

48 You have not submitted any information to fulfil this information requirement.

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

3.3. Study design

3.3.1. Species and route selection

50 According to the test method OECD TG 443, the rat is the preferred species. Therefore, the study must be conducted in the rat.

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

3.3.2. Pre-mating exposure duration

52 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.

53 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.).

54 In this specific case, ten weeks exposure duration is supported by the lipophilicity of the Substance (Log K_{ow} ≥ 4.5) to ensure that the steady state in parental animals has been reached before mating.

55 In your comments to the draft decision, you consider that "*ECHA's request for a ten week pre-mating exposure period does not appear to be justified and a two-week pre-mating exposure period appears to be appropriate for the requested study instead.*" You justify your view with reference to Guidance on IRs & CSA (Chapter R.7a, Appendix R.7.6-3) which states that 'if animals of Cohort 1B in an extended one-generation reproductive toxicity study are mated to produce the F2 generation, then the premating exposure duration will be ten weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility. In these cases, shorter premating exposure duration for parental (P) animals may be considered'.

56 ECHA acknowledges that the Cohort 1B will be extended to produce the F2 generation (see section 3.3.5), and the premating exposure duration for the Cohort 1B animals will be ten weeks. However, ECHA notes that the Substance is lipophilic (Log K_{ow} ≥ 4.5) and the steady state kinetics might be delayed. Therefore, there is no substance-specific justification to shorten the premating exposure duration for the parental (P0) animals (Guidance on IRs & CSA, Chapter R.7a, Appendix R.7.6-3, section 2.1, second paragraph).

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

3.3.3. Dose-level setting

58 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.

59 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.

60 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.

61 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.

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

63 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

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

3.3.4.1. Splenic lymphocyte subpopulation analysis

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

3.3.4.2. Investigations of sexual maturation

66 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.

3.3.5. Extension of Cohort 1B

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

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

69 The use of the Substance reported in the joint submission is leading to significant exposure of consumers and professionals because the Substance is used by professionals as PROCs 0, 1, 2, 3, 4, 5, 7, 8a, 8b, 9, 11, 13, 14, 15, 19 and 28 and consumers as cosmetics, personal care products (leave-on and wash off).

70 Furthermore, there are indications of one or more modes of action related to endocrine disruption because changes in organs and parameters sensitive to endocrine activity are observed. Specifically, the absolute and relative thyroid weights were significantly elevated in the short-term repeated dose toxicity study. In addition, the pre-natal developmental toxicity study (2020, BJ12FM) reports changes related to the Substance in thyroid glands (increase in the incidence of diffuse follicular cell hypertrophy) and changes in thyroid hormone levels (increase in TSH levels and decrease in T3 and T4 levels).

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

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

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

3.3.6. Cohorts 2A and 2B

74 The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.

75 According to the Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 [2]:

(1) "*Substances inducing histopathological changes (i.e., follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring"*.

(2) "*Substances that alter the circulating levels of T3 and/or T4 without histopathological findings would still present a potential concern for neurodevelopment*".

76 Existing information on the Substance itself derived from available short-term repeated dose toxicity and pre-natal developmental toxicity studies show evidence of changes in the thyroid glands (significantly increased absolute and relative thyroid weights, increase in the incidence of diffuse follicular cell hypertrophy) and thyroid hormones (increase in TSH levels and decrease in T3 and T4 levels).

77 For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

3.3.7. Further expansion of the study design

78 No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including 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 IX, 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.

[2] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311; ECHA emphasises that even though the ECHA/EFSA Guidance was developed for hazard identification for endocrine-disrupting properties for other regulatory purposes, the same scientific principles apply also under the REACH Regulation.

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 (2023).
***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 22 February 2023.

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

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

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

In your comments to the draft decision, you requested an extension of the deadline to provide information from 36 to 54 months from the date of adoption of the decision. You justified the request by additional time required to complete the testing due to anticipated delays in performing the EOGRT study. You explain that the current lead times in 3 different contract research organisations is 18 months.

ECHA reminds you that the deadline has been already exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations. Therefore, ECHA has extended the deadline by 6 months, from 36 months to 42 months.

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]
[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 (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).