~~Confidential~~

Helsinki, 09 February 2023

Addressees
Registrants of o-xylene LOA as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
17/02/2021

Registered substance subject to this decision ("the Substance")
Substance name: o-xylene
EC number: 202-422-2

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

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***17 May 2027***.

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

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./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 and 1B (Reproductive toxicity);
    - Cohorts 2A and 2B (Developmental neurotoxicity); and
    - Investigations on learning and memory function as specified in Appendix 1, section 1.3.6.

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 for the decision(s) related to the information under Annex X of REACH

1. Extended one-generation reproductive toxicity study

1 The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

1.1 Information provided to fulfil the information requirement

2 You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the analogue substance p-xylene (EC No. 203-396-5).

3 ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

4 ECHA agrees that an EOGRTS is necessary.

1.2 Grouping of substances and read-across approach

5 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.

6 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).

7 You provide a read-across justification document in IUCLID Section 13. You further submitted an updated justification with your comments on the draft decision.

8 In your read-across justification documents you refer to a group of substances with similar structural and physico-chemical properties and for the extended one-generation reproductive toxicity study endpoint you predict the properties of the Substance from information obtained from the following source substance: p-xylene (EC No. 203-396-5).

9 You define the the structural basis for the analogue approach as "*The registered substances are part of a group of substances with similar structural and physico-chemical properties. Xylene is an aromatic compound, which features a benzene ring, and two methyl groups. There are three structural similar isomers of xylene – meta-, ortho- and para-xylene; the position of the second methyl group in relation to the first differs in the three isomers. Methyl groups are bonded on the benzene ring at the positions of 1 and 3 in m-xylene, 1 and 2 in o-xylene, and 1 and 4 in p-xylene. All xylene isomers and ethylbenzene have the molecular formula C8H10.*"

10 You provide the following reasoning for the prediction of toxicological properties: "*The existence of similar in vivo pathways for metabolism and elimination, coupled with comparable physicochemical and toxicological properties, suggests that read-across from target and source substances for the endpoints related to toxicity and more specifically sub-*

chronic toxicity, developmental toxicity and reproductive toxicity is scientifically justifiable.”.

11 ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

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

1.2.1 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 bridging studies to compare properties of the category members. As indicated above, your read-across hypothesis is based on the assumption that the structurally similar category members cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the category members 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 category members.

15 With a view to your comments to the draft decision concerning the requirement or expectation of what information in particular is needed for a read-across adaptation, and in particular whether an OECD TG 421 or OECD 422 would be a prerequisite for read-across of information on an OECD TG 443 study, ECHA further points out the following.

16 ECHA considers that read-across adpatations based on Annex XI, Section 1.5 commonly require supporting information to demonstrate that the properties of the substances are ‘*likely to be similar or follow a regular pattern as a result of structural similarlity*’. The requirement for adequate and reliable documentation is further emphasised in the last paragraph of that Section 1.5, which among others explicitly refers to ‘*supporting information to scientifically justify such explanation for prediction of properties*’.

17 Depending on the hypothesis of the case, supporting information can take many forms. There is no single “prerequisite” that would fit all cases as supporting information. Such supporting information usually consists of studies of comparable design and duration for the Substance and of the source substance(s) that allow a direct comparison of properties under defined equal conditions (bridging studies). These studies should include information on the impact of all compositional differences between the substances, to allow an assessment of the similarity between the Substance and the source substances. ECHA usually refers to OECD TG 421 or 422 as an example of suitable, commonly used bridging studies for read-across approaches that intend to adapt an OECD TG 443.

18 However, your read-across justification document in IUCLID section 13, or any other document in the registration dossier or in the comments to the draft decision, does not include any robust study summaries or descriptions of data for the other category members that would confirm that all substances cause the same type of effects relevant to this endpoint (sexual function and fertility). In particular, there is for example no lower-tier information in the form of e.g. combined repeated dose- and toxicity to reproduction and development screening tests (OECD TG 422) available for any of the category members, via which their toxicity profiles could be compared to support the read-across.

19 For further clarification, ECHA has taken into consideration the newly provided OECD TG 414 studies and the information from repeated dose toxicity studies, which you also provide in your comments. As these studies cover the developmental toxicity endpoint and organ toxicity without functional element, they do not provide supporting information allowing a comparison of sexual function and fertility effects between the different isomers. In your comments to the draft decision, you also point out that there is a one generation reproduction study with mixed-xylene (1983) which is proposed as supporting information for the read-across approach. However, the one generation reproduction study with mixed-xylene (1983) available in your dossier does not provide supporting information allowing a comparison of sexual function and fertility effects between the different isomers.

20 In the absence of such information, you have not established that the category members, in particular the source substance and the Substance, are likely to have similar properties regarding this endpoint. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across. Furthermore, in the absence of such information, it is currently impossible to determine which substance should be used as the source substance in case you consider adapting the information requirements for the other category members.

1.2.2 Avoiding bias in the prediction

21 In order to make an accurate prediction of ecotoxicological and toxicological properties all relevant information must be considered in the prediction. If not all information is considered in the read-across approach, bias can be introduced in the predictions which may result in an over/underestimation in the prediction (RAAF, 2017; Chapter 4.5.1.5.). Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of study(ies) performed on the source substance(s).

22 You have not provided any information for the three category members that is relevant to the endpoint toxicity to reproduction (fertility) e.g. in the form of screening for reproductive/developmental toxicity studies (OECD TG 421/422) or similar information from other sources.

23 In the absence of such information, it is currently impossible to determine which substance should be used as a source substance in case not all category members are tested in an extended one-generation reproductive toxicity study (OECD TG 443).

24 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.

25 Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under Column 2 nor under the general rules of Annex XI.

1.3 Specification of the study design

1.3.1 Species and route selection

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

27 ECHA considers that the oral route is the most appropriate route of administration, since the Substance to be tested is a liquid.

1.3.2 Pre-mating exposure duration

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

29 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 pre-mating exposure duration (Guidance on IRs & CSA, Appendix R.7.6-3).

1.3.3 Dose-level setting

30 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.

31 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.

32 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.

33 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.

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

35 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.

1.3.4 Cohorts 1A and 1B

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

37 Histopathological investigations in Cohorts 1A and 1B

38 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.

39 Splenic lymphocyte subpopulation analysis

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

41 Investigations of sexual maturation

42 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.

1.3.5 Cohorts 2A and 2B

43 Column 2 of Annex IX/X, Section 8.7.3. to REACH provides that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

44 Existing information on the Substance ([redacted] 2020) and on a substance structurally analogous to the Substance (technical xylene CAS: 1330-20-7 [redacted] 1993, [redacted] 1995, 1997) derived from available in vivo studies provided in the IUCLID sections 7.5.1 and 7.8.2 show evidence of concern on (developmental) neurotoxicity.

45 After prenatal exposure to a substance structurally analogous to the Substance (technical xylene CAS: 1330-20-7), the following effects have been observed in offspring: Impaired performance on a motor ability test (Rotarod) ([redacted] 1993); increased latencies in a Morris water maze after platform relocation at the ages of 16, 28, and 55 weeks ([redacted] 1995); delayed acquisition of air righting reflex, decreased absolute brain weight, and impaired neuromotor performance (Rotarod) and learning/memory (Morris water maze) ([redacted] 1997). Furthermore, after exposure to the Substance in repeated dose toxicity study in rats ([redacted] 2020), both male and females in high dose group exhibited treatment related effects on arousal (hypoactivity or hyperactivity) unusual posture and abnormal gait as well as individual cases of twitching or excessive rearing. All studies are provided in the IUCLID sections 7.5.1 and 7.8.2 of the technical dossier of the Substance o-xylene.

46 You proposed not to include Cohort 2A and 2B.

47 In your comments to the draft decision, you understand that the effects listed above may be considered as potential DNT cohort triggers, but you still do not agree on the need to perform Cohorts 2A and 2B. You also refer to the draft interim report of ECHA´s EOGRTS review project.

48 Regarding your comments on the deviations in the study designs of [redacted], 1993; [redacted], 1995; [redacted] 1997, the concern is still not clarified as results are contradicting. ECHA considers that effects on the central nervous system needs to be clarified for reliable hazard assessment conclusion. Furthermore, you agree with the toxicity seen in the newly perfomed [redacted], 2020; but propose to consider the clinical signs as

transient change. As explained in ECHA Guidance on IRs and CSA R.7a, Appendix R.7.6-2, EOGRTS study design, example of a particular concern justifying inclusion of the Cohort 2A and 2B to EOGRT study design are any signs of behavioural or functional adverse effects on the nervous system in adult studies, eg. clinical and/or behavioural signs (such as abnormal gait, narcosis, seizures or any other altered activity) if seen in absence of general toxicity. ECHA considers that the above mentioned effects seen in the reliable contemporary 90d oral repeated dose toxicity is sign of behavioural or functional adverse effects on the nervous system in adult study.

49 Regarding your comments related to the draft interim report on the EOGRTS review project, it is important to first clarify the objectives of the EOGRTS review project: to evaluate how a sample of studies have been designed and performed with reference to the available OECD TG, guidance and the compliance check decisions requesting them. Therefore, its outcomes are not appropriate to assess other elements such as the general ability to perform adequately the EOGRTS study or the clarity of the existing OECD TG and guidance documents. Furthermore, the main conclusions of the review project are actually contradicting your statement that the issues observed would mainly be the "consequence of the lack of clarity in all the available OECD TG and guidance documents" as most of the issues observed result from not following the existing TG and guidance.

50 Therefore, ECHA concludes that performing new studies is not hampered due to issues identified in the EOGRTS review project´s draft interim report and advises to have the studies performed by test laboratories able to demonstrate proficiency, which will apply methodologies in line with the OECD TG and guidance (in particular on dose level selection) and ensure detailed reporting.

51 Regarding your specific comment on the historical control data (HCD), also the OECD TG 426 can provide useful HCD as long as the investigations are conducted at comparable time points.

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

1.3.6 Cognitive functions: learning and memory

53 Paragraph 51 of OECD 443 provides that, "*If existing information indicates the need for other functional testing (e.g. sensory, social, cognitive), these should be integrated without compromising the integrity of the other evaluations conducted in the study.*"

54 It has been reported that a substance structurally analogous to the Substance (technical xylene CAS: 1330-20-7 containing the Substance, m- and p-xylene, and ethylbenzene) causes impaired learning and memory in a Morris water maze after platform relocation at the ages of 16, 28, and 55 weeks ([redacted] 1995, 1997), which demonstrates adverse effects on spatial learning and memory. In view of the close structural similarity of the constituents of technical xylene to the Substance, coupled to their similar toxicological properties in repeated dose and pre-natal developmental toxicity studies, it is to be expected that technical xylene and the Substance will behave similarly for neurotoxicity effects. It is therefore to be expected that the Substance will cause effects on spatial learning and memory as a specific neurotoxicity, and it is necessary to measure those effects.

55 Therefore, it is necessary to conduct spatial learning and memory tests for F1 animals. The spatial learning and memory tests must be performed in accordance with OECD 426 paragraph 37, i.e. at adolescence (e.g. PND 25-30) and young adulthood (PND 60 and older). With a view to your comments on the Proposal for Amendment concerning the choice of tests at these two time points, ECHA clarifies that, among the tests given in OECD TG 426, paragraph 37, you should conduct the Morris water maze test at both time points since

this has previously been shown to detect effects of technical xylene on learning and memory in [redacted] 1995, 1997.

56 In your comments on the Proposal for Amendment, you further argue (1) that investigations on learning and memory is not covered by the standard information requirement of REACH (2) the integrity of the specific investigations on spatial learning and memory will be compromised, because it is unclear how the specific investigations on spatial learning and memory function will be able to distinguish between developmental neurotoxicity that has manifested during gestation and lactation and effects that are caused by exposure of the offspring to substances (3) [redacted] 1995, 1997 did not use ortho-xylene, but rather technical xylene (CAS: 1330-20-7), and further justification is needed in order to trigger the learning and memory tests with this substance; that ECHA has ignored [redacted] (1986). "Postnatal evaluation of prenatal exposure to p-xylene in the rat." Toxicol Lett 34(2-3):223-229 (4) that ECHA accepts read-across for triggering the learning and memory investigations while rejecting read-across for the EOGRTS study, and this is perplexing.

57 However, (1) the standard information requirement and basis of extension of cohorts 2A and 2B are set out above. According to the introductory part of Annex X of the REACH Regulation, '*[w]here a test method offers flexibility in the study design, for example in relation to the choice of dose levels, the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment.[...]*'. In case the data gap is identified, ECHA has to request studies defined in the relevant provisions of REACH annexes. In such requests, ECHA is competent to define, if necessary, the details of the design to ensure that the generated data for a particular substance is adequate for classification and risk assessment and will achieve compliance of the registration dossier. The requirement for testing of spatial learning and memory arises from paragraph 51 of OECD TG 443, existing information as set out above and is necessary to provide information for classification and risk assessment. (2) The integrity of the investigations will not be compromised on the basis you describe, although the interpretation of the resulting data will be subject to the uncertainty which you describe. (3) ECHA has clarified that [redacted] 1995, 1997 used technical xylene, and has provided justification to trigger the learning and memory investigations for the Substance. The results from [redacted] 1986 address a different memory paradigm and do not over-ride the concern raised by [redacted] 1995, 1997. (4) ECHA considers that information from structurally related substances may give rise to concern about a substance, even though the criteria for read-across between the structurally related substance and the substance, according to Annex XI, Section 1.5, are not met.

1.3.6.1 Observations for the spatial learning and memory testing

58 OECD TG 426, paragraph 37 presents examples of test methods for different types of associative learning and memory. Among the tests given in OECD TG 426, paragraph 37, you should conduct the Morris water maze test at both time points since this has previously been shown to detect effects of technical xylene on learning and memory in [redacted] 1995, 1997. The Morris water maze is suitable to investigate spatial learning and memory and can be adapted to both adolescence and young adulthood [1-3].

59 Investigations of spatial learning and memory should not compromise the integrity of the study. In OECD TG 443 adverse effects on sexual function and fertility may limit the number of offspring available for developmental investigations. Dosing must be based on the considerations provided above ('Dose-level setting'), and dosing must not be lowered in order to get a sufficient number of offspring. The priority of the OECD TG 443 test is to identify potential effects on sexual function and fertility.

60 Taking into account the practical aspects of conducting the OECD TG 443 study, as an alternative to Cohort 2A, the investigations on spatial learning and memory may also be

conducted in Cohort 1A animals which can be allocated to two sets of animals, 10 males and 10 females in both; the first set of animals to be tested at adolescence and the other set of animals at young adulthood.

61 In your comments on the Proposal for Amendment, (5) you have questioned why two different tests should be performed, and you have raised concerns about the appropriateness and validation of the Cincinnati water maze test (6) you argue that there are concerns about conducting the Morris water maze in weanling (PND 25±2) rats (7) you argue that Morris water maze is performed rarely, in 9/101 DNT tests using 2014 data (8) you argue that no CRO offers the Morris water maze test (9) you argue that the learning and memory tests are additional testing which cause stress to the animals.

62 ECHA agrees with your (5) concerns related to different tests at the two time points, and asks for testing with one test, the Morris water maze. However, (6) Reference [3] in the below specifically addresses the use of young rats in the Morris water maze. Further we have clarified that testing performed at adolescence may be at e.g. PND 25-30. (7) We note that the Morris water maze has been performed in significant number of DNT studies (8) ECHA notes that for example [redacted] considers that the Morris water maze has been validated using positive control substances, and used extensively in regulatory studies, so a large database exists with historical control data (9) as set out above, the conduct of the learning and memory investigations follows from the requirements of the Test Guideline 443, in conjunction with the OECD TG 426.

[1] Vorhees and Williams (2015) Reprint of "Value of water mazes for assessing spatial and egocentric learning and memory in rodent basic research and regulatory studies". *Neurotoxicol Teratol*. 52, 93-108.

[2] Vorhees and Makris (2015) Assessment of learning, memory, and attention in developmental neurotoxicity regulatory studies: synthesis, commentary, and recommendations. *Neurotoxicol Teratol*. 52, 109-115.

[3] Vorhees and Williams (2014) Assessing Spatial Learning and Memory in Rodents. ILAR Journal 55, 310-332.

1.4 Outcome

63 Your testing proposal is rejected under Article 40(3)(d) of REACH. Under Article 40(3)(c) you are requested to carry out the additional test with the Substance, as specified above.

1.4.1 Further expansion of the study design

64 The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, 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

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 11 March 2021.

ECHA held a third party consultation for the testing proposal(s) from 22 April 2021 until 7 June 2021. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 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. Moreover, you asked for further extension of the deadline of the decision, and provided written justification from a CRO. An additional extension of 12 months was granted.

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).

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the initial draft decision by re-sending your initial comments as a separate file, as well as a separate file with comments on other substances These comments do not address the proposed amendment(s). Therefore, these comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-81 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

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

1.2. Test material

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

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- 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[3].

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