~~Confidential~~

Helsinki, 09 September 2022

Addressees
Registrant(s) of Vinyl Acetate JS [203-545-4] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
27/04/2020

Registered substance subject to this decision ("the Substance")
Substance name: Vinyl acetate
EC number: 203-545-4
CAS number: 108-05-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***16 June 2025***.

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

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

1. Same in vivo genetic toxicity study requested below in B.1

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

1. In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) combined with in vivo mammalian erythrocyte micronucleus test (test method: OECD TG 474) in rats, oral route. For the comet assay the following tissues shall be analysed: liver, glandular stomach and duodenum.

Reasons for the request(s) are explained in the following appendices entitled "Reasons to request information required under Annexes VIII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- 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.

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

ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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

[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 A: Reasons to request information required under Annex VIII of REACH

1. *In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test*

Under Annex VIII, Section 8.4, column 2 of REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

a) Triggering of in vivo mutagenicity studies

Your dossier contains positive results for the *in vitro* cytogenicity tests and *in vitro* gene mutation study in mammalian cells which raise the concerns for chromosomal aberration and gene mutation. Furthermore, the *in vivo* studies submitted in your dossier are inadequate studies for the reasons described under Section B.1.

Based on the information in your dossier, ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concerns identified *in vitro*.

b) Information provided to fulfil the information requirement

In your comments to the draft decision, you agree that *in vitro* testing has identified a mutagenic potential for the Substance. However, you consider that the *in vitro* results does not reflect realistic *in vivo* exposures. You also claim that a threshold for mutagenicity has been identified for the Substance. In support of your claim, you provide the following information:

i. a reference to a publication on the formation and loss of DNA adducts in nasal, olfactory tissues and peripheral monocytes (PBMC) in rats exposed to vinyl acetate monomer through inhalation for 6 hours ([redacted] 2021)[2]
ii. a reference to a manuscript submitted for publication on DNA adducts in liver, brain and bone marrow in rats exposed to vinyl acetate monomer through inhalation for 14 days ([redacted] unpublished)[3]

We understand that, you base your argument on section R.7.7.6.3 of ECHA guidance R.7a.

We have asseded this additional information from your comments to the draft decision and identified the following issue:

1) The references above cannot be seen as valid supporting evidence for your claim

According to the ECHA guidance R.7a (R.7.7.6.3, p 570) following a positive result in an *in vitro* test, "*adequately conducted somatic cell in vivo testing is required to ascertain if this potential can be expressed in vivo. In cases where it can be sufficiently deduced that a positive in vitro finding is not relevant for in vivo situations (e.g. due to the effect of the test substances on pH or cell viability, in vitro-specific metabolism: see also Section R.7.7.4.1), or where a clear threshold mechanism coming into play only at high concentrations that will not be reached in vivo has been identified (e.g. damage to non-DNA targets at high concentrations), in vivo testing will not be necessary.*"

You state that the DNA adduct studies via the inhalation route (i. and ii.) "*define a threshold for potential genotoxicity".*

2 [redacted]
3 [redacted]

However, ECHA notes that no considerations on the identification of potential thresholds for genotoxicity are reported in these studies. You have not either demonstrated how the new information show that a clear threshold mechanism comes into play only at such high *in vitro* concentrations that those would not be reached *in vivo.* Finally, you have not justified how this information generated via the inhalation route would be of relevance to potential genotoxicity via the oral route. Therefore, your justification does not provide a valid basis to omit the study. As a result, ECHA maintains that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concerns identified *in vitro*.

For the assessment and the specifications of the study to be performed, see the request B.1. Moreover, your other comments to the draft decision regarding this information requirement are addressed under the request B.1.

Appendix B: Reasons to request information required under Annex IX of REACH

1. *In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test*

Under Annex IX, Section 8.4, column 2 of REACH, the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered if 1) there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and 2) there are no appropriate results already available from an *in vivo* somatic cell genotoxicity study.

a) Triggering of in vivo mutagenicity studies

In relation to the first condition, your dossier contains positive results for the *in vitro* cytogenicity tests and for the *in vitro* gene mutation study in mammalian cells which raise the concerns for gene mutation and chromosomal aberration.

In your comments to the draft decision, you agree that *in vitro* testing has identified a mutagenic potential for the Substance. However, you consider that the *in vitro* results does not reflect realistic *in vivo* exposures and that there is a threshold for mutagenicity identified for the Substance.

For the reasons already explained under request A.1., ECHA maintains that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concerns identified *in vitro*.

In relation to the second condition, your dossier contains the following *in vivo* studies:

i. *In vivo* mammalian erythrocyte micronucleus test similar to OECD 474, non-GLP (Maki-Paakkanen & Norppa, 1987)
ii. *In vivo* micronuclei in germ cells of male mice, non-guideline, non GLP (Lahdetie, 1988)

We have assessed the information provided in your dossier in relation to the second condition and we identified the following issue:

To be considered adequate, the study has to meet the requirements of OECD TG 474, and the key parameters of this test guideline include:

1) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow (e.g. a reduction in the proportion of immature erythrocytes among total erythrocytes in the bone marrow or peripheral blood).
2) The proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood).
3) At least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes.
4) The proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes must be reported for each group of animals.

Study (i.) is performed with a guideline similar to OECD 474 and study (ii.) is not performed according to any guideline. These studies can be considered as a follow up to one of the concerns raised by the *in vitro* results, i.e. chromosomal aberration. However, the above mentioned key parameter(s) are not met, because the reported data for the studies do not include:

1) a maximum studied dose that is a MTD or induces toxicity

2) and 3) the analysis of the adequate number of cells
4) data on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

The information provided in your dossier does not cover the key parameters required by OECD TG 474.

In your comments to the draft decision, you claim that the studies (i. and ii.) are equivalent to the guideline at the time the studies were performed and therefore "*the information requirement for in vivo genotoxicity is adequately addressed in the existing dossier*". However, the REACH Regulation addresses "use of existing data" as an adaptation under section 1.1 of Annex XI. More specifically, section 1.1.2 set out the conditions to use existing data on human health and environmental properties from experiments. You have submitted the studies carried out in accordance with the specification of older or different test methods form those currently applicable without submitting a valid adaptation fulfilling the conditions set out in section 1.1.2. In addition, in your comments you do not provide any specific information addressing the issues identified above for the *in vivo* studies (i. and ii.) in your comments.

Therefore, the studies i. and ii. you submitted cannot be considered as providing appropriate results already available from an *in vivo* somatic cell genotoxicity study. Consequently, the conditions set out in Annex IX, Section 8.4, column 2 are met and the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered.

b) Information provided to fulfil the information requirement

As already explained above, you have not provided information in your registration dossier that fulfils the information requirement. However, in your comments to the draft decision, you state that *"a combined comet and micronucleus test should not be required"*. You further argue that *"Performing a combined comet assay and micronucleus test with VAM is an unnecessary use of animals".* In support of your claim, you provide the following information:

i. a claim that there is a lack of systemic *in vivo* genotoxic potential related to the Substance via inhalation route based on toxicokinetic information derived from two publications ([redacted] 2021)[2,3]. Hence, you argue that new *in vivo* genotoxicity testing is not necessary.
ii. a claim that the "*conclusions reached during substance evaluation, together with recent (2021) studies that define a threshold for potential genotoxicity"* based on the SEV conclusion and evaluation report for Vinyl acetate (EC 203-545-4), 1 October 2020;
iii. a reference to a publication on formation and loss of DNA adducts in rats exposed to vinyl acetate monomer through inhalation for 6 hours in nasal, olfactory tissues and peripheral monocytes (PBMC) ([redacted] 2021)[2]
iv. reference to a manuscript submitted for publication on DNA adducts in rats exposed to vinyl acetate monomer through inhalation for 14 days in liver, brain and bone marrow from ([redacted], unpublished)[3];

ECHA has assessed the information from your comments to the draft decision and identified the following issues:

1) Your justification under point i. is not of relevance for the oral route

The OECD 474, para 10. states that "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*".

However, you have not explained how lack of systemic *in vivo* genotoxic potential via the inhalation route is relevant for the systemic *in vivo* potential via the oral route. You have neither demonstrated (*e.g.*, by measurement of the plasma or blood levels of the Substance) that the Substance and its metabolite(s) are not systemically distributed in biologically meaningful concentrations and hence would not reach the bone marrow when administered via the oral route.

Therefore, you have not demonstrated that the requested study to be performed via the oral can be omitted.

2) Your claim under point ii. is not a valid basis to omit the information requirement

The REACH Regulation enables registrants to adapt information requirements only under the conditions explicitly prescribed in its Annex XI and column 2 of its Annexes VII to X.

In your comments to the draft decision you state that under substance evaluation, it was concluded that there is "*no need for regulatory follow-up action at EU level*" and that you consider "*it inappropriate to ignore the SEv conclusion and now request new vertebrate animal genotoxicity testing on vinyl acetate*".

ECHA notes that this claim does not relate to any of the adaptations ste out in Annex XI and column 2 of its Annexes VII to X. In addition, mutagenicity was not an identified concern for the SEV and hence it was reported as "*not assessed comprehensively*" in the substance evaluation conclusion and evaluation report. ECHA reminds that the SEV report is an opinion of the evaluating Member State and that the statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage, based on information submitted in application of a compliance check decision.

3) The studies references iii. and iv. do not meet the information requirement

The ECHA guidance R.7a states that following a positive result in an *in vitro* test, "*adequately conducted somatic cell in vivo testing is required to ascertain if this potential can be expressed in vivo. In cases where it can be sufficiently deduced that a positive in vitro finding is not relevant for in vivo situations (e.g. due to the effect of the test substances on pH or cell viability, in vitro-specific metabolism: see also Section R.7.7.4.1), or where a clear threshold mechanism coming into play only at high concentrations that will not be reached in vivo has been identified (e.g. damage to non-DNA targets at high concentrations), in vivo testing will not be necessary.*"

In your comments to the draft decision you state that recent (2021) inhalation DNA adduct studies (iii. and iv.) "*define a threshold for potential genotoxicity".* You further state that the DNA adduct data addresses the need for additional *in vivo* genotoxicity testing and shall be used to fulfil the information requirement.

As already explained under request A.1., you have not demonstrated how the new information show a clear threshold mechanism coming into play only at high concentrations *in vitro* that will not be reached *in vivo* and how this information generated via the inhalation route would be of relevance to potential genotoxicity via the oral route. Therefore, studies iii. and iv. cannot be regarded as providing a valid basis to omit the study. ECHA also notes that, the results of the studies raise a concern for gene mutation in some of the tissues studied.

On this basis, the information requirement is not fulfilled.

i. Test selection

The positive *in vitro* results available in the dossier indicate a concern for both chromosomal aberration and gene mutation. According to the ECHA Guidance R.7a, Section R.7.7.6.3, the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) is a genotoxicity indicator test that is suitable to follow up the positive *in vitro* result for both chromosomal aberration and gene mutation. However, the *in vivo* mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) is a mutagenicity test that provides evidence of *in vivo* chromosomal mutagenicity, as the study detects both structural and numerical chromosomal aberrations. As also indicated in the ECHA Guidance, it is possible to combine the comet assay and the MN test into a single study. Please note that, at the 70th meeting of the Member States Committee (MSC-70) (June 2020) , it was agreed that the combined study of the comet assay and the MN test would be most suitable when both concerns for chromosomal aberration and gene mutation exist and no appropriate *in vivo* genotoxicity data are available in the dossier addressing both the chromosomal aberration and gene mutation concern. The combined study can help reduce the number of tests performed and the number of animals used while addressing both chromosomal aberration and gene mutation. Therefore, the comet assay combined with the MN test is the most appropriate study for the Substance.

In your comments to the draft decision, you state that the *"interpretation of the comet assay is unreliable and potentially misleading, particularly at cytotoxic doses, the DNA adduct biomarker studies are highly specific, unambiguous, definitive in identifying a genotoxic threshold, and are not confounded by cytotoxicity".*

ECHA notes that it is known that cytotoxicity can have an impact on the result of the comet assay (e.g. false positive). The recommended protocol described in OECD TG 489 makes clear that cytotoxicity must be monitored closely (measurement of cytotoxicity in the collected cells, and also need for histopathological analysis in case of increase in % tail DNA) in order to rule out the influence of cytotoxicity.

ii. Test design

According to the test method OECD TG 489, the test must be performed in rats. Therefore, the combined test (OECD TG 489 and OECD TG 474) must be performed in rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In the comments to the draft decision you disagree with performing the combined test via the oral route. You consider that the oral route of exposure is not relevant for the Substance in the combined comet and micronucleus assay. You refer to the SCHER (2008), EU RAR (2008) and SEv (2020) reports concluding the oral route as not being "*a relevant route of human exposure for either occupational workers or consumers, due to"* the Substance's "*volatility and negligible presence in consumer goods*".

However, according to the RCRs provided in your CSR, there is significant exposure via both the dermal and inhalation routes in a number of exposure scenarios. In exposure scenario 1, contributing scenario 4, for example, the combined routes systemic RCR is [redacted], compared with the equivalent RCR for inhalation of [redacted]. In this contributing scenario, the inhalation exposure is only the minor contributor to the combined routes exposure. Recognition of SCHER (2008), EU RAR (2008), SEv (2020) reports do not remove the fact that the Substance is a liquid, which vapour pressure at 20˚C is 11,300 Pa. ECHA Guidance refers to a vapour pressure >25,000Pa for the inhalation route becoming appropriate. Furthermore, the Substance has the Hazard Statement H335 (H335: May cause respiratory irritation) and Acute Tox. 4 (H332: Harmful if inhaled). As the Substance causes respiratory irritation and the

vapour pressure is below 25,000Pa, the oral route is considered an appropriate route to maximise the internal dose. Finally, in your registration dossier, the robust study summary for the PNDT study in rabbit ([redacted], 2018), you also state that "*the oral route of exposure was selected because this is a possible route of human exposure during manufacture, handling or use of the test item, this was the preferred route of administration for developmental toxicity testing in rabbits, and was the route of administration requested by ECHA"*. Hence, the information provided in your comments does not change the assessment and the appropriateness of oral route of administration.

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

The combination of OECD TGs 489 and 474 should not impair the validity of and the results from each individual study. Careful consideration should be given to the dosing, and tissue sampling for comet analysis alongside the requirements of tissue sampling for the mammalian erythrocyte micronucleus test (see OECD TG 489, e.g. Bowen *et al*. 2011[4]).

You are reminded that for the comet assay you may decide to take into account the potential cross-linking properties of the Substance in the experimental setup of the comet assay and perform, additionally to the standard comet assay, a modified comet assay in order to detect cross links. Therefore, you may consider preparing and analysing two sets of slides: one set of slides submitted to the standard experimental conditions (as described in OECD TG 489); the other set of slides submitted to modified experimental conditions that enable the detection of DNA. The modified experimental conditions may utilise one of the following options: (1) increase of electrophoresis time, e.g. as described in reference 23[5] in the OECD TG 489; (2) treatment of isolated cells (either in suspension or embedded in the slides) with a chemical (e.g. MMS); or (3) treatment of isolated cells (either in suspension or embedded in the slides) with ionising radiation (options 2 and 3 are described e.g. in references 36-39[6] in the OECD TG 489 or Pant[7] et al. 2015). In order to ensure the robustness of the test result a specific positive control group of animals would be needed.

In the comments to the draft decision you claim that the modified comet assay detecting potential cross-linking properties of the Substance is not applicable to determine the

[4] Bowen D.E. et al. 2011. Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the comet assay and the flow-cytometric peripheral blood micronucleus test. Mutation Research 722 7–19

[5] Reference 23 of OECD TG 489 (2016): (23) Nesslany, F, Zennouche N, Simar-Meintieres S, Talahari I, NKili-Mboui E-N, Marzin D (2007), *In vivo* comet assay on isolated kidney cells to distinguish genotoxic carcinogens from epigenetic carcinogens or cytotoxic compounds, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Vol. 630/1, pp. 28-41.

[6] References 36 to 39 of OECD TG 489 (2016): (36) Merk, O., G. Speit (1999), Detection of crosslinks with the comet assay in relationship to genotoxicity and cytotoxicity, Environmental and Molecular Mutagenesis, Vol. 33/2, pp. 167-72; (37) Pfuhler, S., H.U. Wolf (1996), Detection of DNA-crosslinking agents with the alkaline comet assay, Environmental and Molecular Mutagenesis, Vol. 27/3, pp. 196-201; (38) Wu, J.H., N.J. Jones (2012), Assessment of DNA interstrand crosslinks using the modified alkaline comet assay, Methods in Molecular Biology, Vol. 817, pp. 165-81; (39) Spanswick, V.J., J.M. Hartley, J.A. Hartley (2010), Measurement of DNA interstrand crosslinking in individual cells using the Single Cell Gel Electrophoresis (Comet) assay, Methods in Molecular Biology, Vol. 613, pp. 267-282.

[7] Pant K, Roden N, Zhang C, Bruce C, Wood C, and Pendino K (2015) Modified *In Vivo* Comet Assay Detects the Genotoxic Potential of14-Hydroxycodeinone, an a,b-Unsaturated Ketone in Oxycodone. Environmental and Molecular Mutagenesis 56, 777-787.

properties of vinyl acetate. However, ECHA in this decision request the standard comet assay which is subject to the information requirement. Nevertheless, you may take into account potential cross-linking properties of the substance and consider to perform a modified comet assay.

iii. Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483, depending on the concern raised by the substance) may still be required under Annex IX/X of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

Therefore, you may consider to collect the male gonadal cells collected from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, in accordance to Annex IX/X, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

In your comments to the draft decision you state that inhaled Substance "*cannot induce in vivo germ cell mutagenicity, as it is not systemically distributed in biologically meaningful concentrations*". However, 'germ cell mutagenicity' is the name of the hazard class according to CLP. It does not mean that the classification for mutagenicity can be warranted only if there are data on germ cells. If positive data are obtained on somatic cells only, such data can warrant a classification as 'germ cell mutagenicity' Category 2.

In relation to your statement above you refer to the acute [redacted] (2021)[8] study performed via inhalation route which quantified only minor systemic distribution to PBMCs (peripheral blood monocytes) at the highest concentrations tested. You claim that neither the Substance nor its metabolites reach the germ cells.

ECHA understands that you intend to show that the presence of the Substance and its metabolite(s) in blood and other systemic organs is low. You have provided DNA adduct studies which are indicative of lower DNA adduct levels in systemic organs after inhalation exposure. However, you have not provided any measurement of the plasma or blood levels of the test substance to substantiate your claim that the Substance and its metabolite(s) is not detectable in blood and does not reach systemic organs. Moreover, ECHA also understands that the [redacted] (2021) publication states that "*VAM or its metabolite may enter into systemic circulation to potentially damage tissues beyond nasal Epithelium"* indicative of systemic availability.

8 [redacted]

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[9].

B. 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[10].

[9] https://echa.europa.eu/practical-guides
[10] https://echa.europa.eu/manuals

Appendix D: 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 3 February 2021.

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

ECHA took into account your comments did not amend the request(s).

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.

Appendix E: List of references - ECHA Guidance[11] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[13]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[14]

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[12] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[13] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
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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.