EUROPEAN CHEMICALS AGENCY

Helsinki, 13 January 2021

Addressees
Registrants of Dioxolane Registration listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
03/10/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,3-dioxolane
EC number: 211-463-5
CAS number: 646-06-0

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***19 April 2024***.

A. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route specified as follows:

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation and**
   - **Cohort 3 (Developmental immunotoxicity).**

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

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 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.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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 Christel Schilliger-Musset, 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 for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore, Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

A. Your adaptation under Column 2, Section 8.7 of Annex X

You have adapted the information requirement based on Column 2, Section 8.7 of Annex X.

According to Annex X, Section 8.7., Column 2, second paragraph, the study does not need to be conducted if the substance meets the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment [...] However, testing for effects on fertility must be considered.

You refer to the above adaptation by stating that *"no studies need to be conducted if a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment."*

You consider that the Substance meets the the criteria for classification as toxic for reproduction category 1B (Repr 1B): May damage the unborn child (H360D). To support your view, you have provided an expert assessment:

> *Expert Statement by Dr W. Faber waiving EOGRTS (OECD 443), 2017: Review of 1,3-dioxolane rat and rabbit developmental toxicity studies and justification for classification and labelling by the GHS system"*

Referring to this expert assessment you state that: *"Taking all submitted data on reproductive toxicity into consideration, 1,3-dioxolane is considered to be meeting the criteria for classification as toxic for reproduction category 1B: May damage the unborn child (H360D)(see Section 13.2 expert assessment, Faber (2017))."*

We have evaluated your adaptation and identified the following deficiencies:

1) The Substance is self-classified by you as Repr. 1B without specification for sexual function and fertility (F) or developmental toxicity (D). In the expert assessment of Faber (2017) only prenatal developmental toxicity studies have been assessed and the assessment concludes that the prenatal developmental toxicity findings meet the criteria for reproductive toxicity category 1B. This assessment supports your classification as Repr. 1B (H360D), i.e. for development. On the contrary, sexual function and fertility are not covered by this classification, and the adaptation specifically requires that testing for effects on fertility must be considered. We have evaluated the sexual function and fertility below under Section B. Weight of evidence.

2) You do not justify that you have adequate data to support a robust risk assessment.

In conclusion, your adaptation cannot be accepted as a valid adaptation for sexual function and fertility under the current information requirement.

B. Weight of evidence

You have provided more than two sources of information for the information requirement, including the expert assessments and a USEPA HPV Challenge Program Submission document on 1,3-dioxolane, and you have named some of your sources of information as "WoE". While you have not claimed a specific adaptation, ECHA has evaluated the provided information according to Annex XI, Section 1.2 of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information obtained with the Substance:

Studies and study summaries

i. *WoE:* [redacted] *- One-generation inhalation studies, combines information from two studies:*
- *KS: Single generation reproduction study with the vapors of dioxolane in albino rats: Results of the F0 and F1a generations,* [redacted] *study report (1976)*
- *KS: Single generation reproduction study with the vapors of dioxolane in albino rats: Results of the F0 and F1b generations,* [redacted] *study report (1976)*

ii. *WoE:* [redacted] *– One-generation drinking water studies (1976), combines information from two studies:*
- *KS: One-generation reproductive study with dioxolane in drinking water of albino rats - Results of (F0) generation* [redacted] *study report (1976a)*
- *WoE* [redacted] *One-generation drinking water study, high dose (1975, 1976b)*

iii. *WoE:* 1,3-dioxolane: 13-week vapor inhalation toxicology study in Fischer 344 rats. [redacted] (1990)

All the original studies for (*i.*) and (*ii.*) above have been conducted in [redacted] during 1975-1976.

Assessments

iv. *EPA HPV Dioxolane assessment 2000: "USEPA HPV Challenge Program Submission, 20 November 2000, Submitted by* [redacted] *"*

v. *Expert Assessment on Fertility by Dr J. Buschmann, 2018: "Assessment on Fertility Effects of Dioxolane (CAS 646-06-0, EC 211-463-5)"*

Source (*iv.*) is the industry's response from 2000 to the EPA challenge to define the toxicologically relevant data set within the HPV guidelines. Source (*v.*) is an assessment of the original data detailed above (*i.*, *ii.*, and *iii.*).

Based on the presented sources of information, you state that the available data gives sufficient information to conclude on the reproductive toxicity (sexual function and fertility) of the Substance.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You present assessments (*iv., v.*) to justify why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has not a particular dangerous property investigated by the required study.

However, these assessments have been prepared for different purposes. The source of information (*iv.*) is meant for toxicity screening (*"screening-level health and environmental effects"*). The assessment (*v.*) refers to the assessment (*iv.*) and states that *"Dioxolane is not a significant reproductive toxicant"* and *"No additional studies are recommended"*. Neither the assessment (*iv.*) nor the assessment (*v.*) does weigh the evidence individually or together and lead to the conclusion that the Substance has or has not a particular dangerous property.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support a weight of evidence adaptation for the information requirement of Section 8.7.3 at Annex X includes similar information to that produced by the OECD TG 443 design as specified in this decision. At general level, it includes information on 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity - and 4) if column 2 triggers are met, also information on sexual function and fertility of the offspring, toxicity to F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

Sexual function and fertility

Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The sources of information (*i., ii.)* provide relevant information on sexual function and fertility, in particular, regarding functional fertility of males and females (*i., ii.*) and investigations of reproductive organs in males (*i.*) and in females (*ii.*). Repeated dose toxicity study (*iii.*) provides relevant information on integrity of reproductive organs in both sexes.

Sources (*iv., v.*) are assessments of the original data (*i., ii.,* and *iii.*), and source (*v.*) also

copies statements from source (*iv.*). Therefore, sources (*iv.* and *v.*) do not bring any new information for the dossier and the evaluation of the weight of evidence adaptation is based on the original sources of information (under *i., ii. and iii.*).

The sources of information (*i., ii., iii.*) have the following deficiencies (1-4) affecting their reliability.

1. Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) must be investigated in parental P0 animals during a continuous exposure from premating until termination, and after at least ten weeks premating exposure duration to ensure steady state of the Substance in parental animals and the coverage of full spermatogenesis and folliculogenesis before mating as indicated in ECHA guidance[2].

   Information provided contains two one-generation studies, one exposing via inhalation route (*i.*) and the other via drinking water (*ii.*). Both studies had two (consequent) matings, for F1a and F1b offspring, but the exposure periods (and investigations, see above) differed. In the inhalation study, exposure of the dams was deficient, lacking exposure during premating period, delivery and lactation. Thus, the study (*i.*) cannot provide reliable information on female functional fertility. In the drinking water study (*ii.*) using low doses, females were not exposed during premating period, and thus, information on female functional fertility is deficient. Furthermore, in the drinking water study using high doses, it seems that for F1a mating the females were exposed to low doses and before F1b mating to high doses, but exposure did not continue after F1b mating started. Thus, functional fertility was not investigated with premating exposure duration in females at low doses and only with premating exposure in females at high doses. In addition, the necropsy findings in females are unreliable because necropsy was conducted after an unexposed period and oestrus cycle and sperm parameters were not investigated in any of the studies.

   In summary, information on functional fertility from exposure starting premating and continuing constantly until weaning of the offspring and termination is not available for females. Therefore, these results are not reliable.

2. Statistical power of the information (number of animals) from the relevant sources of information must be on the similar range than that foreseen to be investigated in an OECD TG 443 with the study design specified in this request.

   The number of females in information sources (*i., ii.* and *iii.*) is 10, instead of 20, as indicated in OECD TG 443. The number of breeding males were 5 (*i., ii.*) or 10 (*iii.*).

   The studies (*i., ii.* and *ii.*) have not investigated the dangerous properties at the similar range of the statistical power as required in the OECD TG 443 as explained above, and therefore, the results are not reliable.

3. At least one of the relevant sources of information must follow the rules for setting the dose levels in the test method and ECHA guidance, demonstrating a dose-response relationship, and be adequate for hazard classification and/or risk assessment.

   The study (*i.*) via inhalation route has not investigated the dangerous properties using dose levels demonstrating a dose-response relationship as required in the OECD TG 443 as explained above, and therefore, the results via inhalation are not reliable.

[2] ECHA Guidance R.7a, Section R.7.6

4. The reliability of the studies conducted in Industrial Bio-Test laboratories during certain period of time have not been confirmed by an independent audit or validation.

   More specifically, extensive amount (71%; 618 out of 867) of the non-acute toxicity studies conducted during the 1960's and until 1978 in [redacted] were found invalid during a post-hoc audit program (see Manual for investigation of HPV chemicals, Chapter 3, Section 3.1.8: Acceptance and sue of studies from Industrial Bio-test laboratories http://www.oecd.org/chemicalsafety/risk-assessment/49191960.pdf.

   The document proposes the following considerations when such an IBT study should be rejected, according paragraph 45: "*In cases where there are no other studies available with which to compare, it is unlikely that an IBT study which has not been audited/ validated could be considered to provide anything more than weak evidence. Depending on the programme this situation may lead to a conclusion that there are data requirements. Where there is no independent audit/validation and the IBT study findings are inconsistent with other data then the study should be rejected.*"

   All the generation studies (studies under *i.* and *ii.*) have been conducted in [redacted] in 1975-1976.

   There are no other generation studies to compare the results from IBT studies. There is no information that the studies presented in the dossier have been audited/validated by any regulatory authority.

   Sources (*i.*) and (*ii.*) cannot be considered reliable because they were conducted in [redacted] in 1975-1976 and have not been audited/validated by any regulatory authority.

   In addition, we note that EPA has published a newer assessment (2009) on the toxicity of the Substance after your source (*iv.*). The IBT studies were assessed in this newer assessment by US-EPA ([redacted] by US-EPA (http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.175.5281&rep=rep1&type=pdf). The assessment states that, based on the Manual for investigation of HPV Chemicals (see above), "*when the study has not been audited by either EPA or FDA, and if the findings of the IBT study were consistent with a study conducted at a later date in another laboratory, then the data may be used but should be considered as weak evidence. In this case, the IBT studies are supported by an independent reference (Sitarek et al., 1992) and data from a dominant lethal assay in rats.*"

   However, in the study from Sitarek *et al.*, (1992) dams are exposed only during gestation, and it cannot be considered similar to generation studies, it provides information on maintenance of pregnancy only. A dominant lethal assay provides very limited information on sexual function and fertility (dominant lethal effect) and males only are exposed. Thus, results from Sitarek *et al.*, and dominant lethal assay can provide only very limited support regarding sexual function and fertility aspects. As there is no generation data from reliable source(s), the reliability of the IBT studies cannot be confirmed, and the results from these studies cannot be used to support evaluation of reproductive toxicity, sexual function and fertility.

   Furthermore, even if the one-generation studies from the [redacted] were from a reliable laboratory, they lack relevant parameters, have a low statistical power, and limited exposure durations, as shown above.

Conclusion on sexual function and fertility

In conclusion, all the generation studies (under *i.* and *ii.*) are unreliable and of no value in a weight of evidence adaptation, and the only relevant and reliable information left for sexual function and fertility is the information on reproductive organs as investigated in source (*iii.*). Information is totally lacking on functional fertility (such as mating, fertility, and parturition), lactation, nursing and litter sizes.

In the absence of reliable information on most of the key elements of sexual function and fertility, all of those related to functional fertility, no conclusion can be drawn on sexual function and fertility.

Toxicity to the offspring

Toxicity to offspring must cover information on deaths before, during or after birth, growth , external malformations, clinical signs, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

The sources of information (*i., ii.*) provide some information on toxicity to the offpsring up to weaning. However, none of the studies have investigations until adulthood of the F1 generation (offspring).

Information provided on toxicity to offspring is limited. None of the sources of information (*i.-iii.*) inform on toxicity to the offspring up to the adulthood, as indicated in the OECD TG 443. Therefore, relevant information is lacking.

Systemic toxicity

Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and histopathology of non-reproductive organs (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

The sources of information (*i.-iii.*) provide relevant, although limited, information on systemic toxicity.

The source of information (*iii.*) inform on systemic toxicity in P0 adults similar to OECD TG 413, and another source of information (*ii.*) provides some information limited on some organ weights and histopathology.

Information provided on systemic toxicity is limited to information from P0 generation and there is no information on systemic toxicity from F1 generation, such as clinical signs, body weights, haematology, clinical chemistry, organs weights and histopathology of non-reproductive organs in adulthood. Without such information no conclusions on the systemic toxicity in F1 generation and its relationship with reproductive toxicity can be made.

In conclusion, information on systemic toxicity is totally lacking from F1 generation from weaning until adulthood. Furthermore, information for P0 systemic toxicity is limited after oral administration.

Information on triggered investigations

If column 2 triggers are met, information on sexual function and fertility of the offspring, developmental toxicity in F2 generation, developmental neurotoxicity and/or developmental

immunotoxicity is relevant. Developmental immunotoxicity includes splenic lymphocyte subpopulation analysis, T-cell dependant antibody response assay, assessment of imune organs and other potential asepcts of developmental immunotoxicity.

The criteria according to column 2 of Section 8.7.3 of Annex X are met to include the Cohort 3 (developmental immunotoxicity) based on the available data on the Substance (see below).

However, you have not provided any information on developmental immunotoxicity. Instead, you have provided a justification for data waiving regarding "immunotoxic potential": *"A conclusion of "immunotoxic potential" is not warranted."* We have evaluated your justification under The specifications for the study design, "Cohort 3" requirement below.

Conclusion on weight of evidence

Taken together, the sources of information as indicated above provide relevant information on

- sexual function and fertility on parental P0 generation but its reliability is affected by insufficient exposure duration, dose levels, low number of animals, and unreliable conducting laboratory.
- toxicity to offspring, but lacking information on relevant life stages of the F1 generation (post-natal period up to adulthood).
- systemic toxicity, but is limited for the parental generation and lacking for the F1 generation from post-natal period up to adulthood.

Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity in order to conclude on these aspects.

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study.

Based on the above, your adaptation is rejected and the information you provided does not fulfil the information requirement.

In your comments to the draft decision, you agree to conduct the requested OECD TG 443 study with the Substance. In relation to your comments on the Cohort 3, please refer below. In relation to your comments on the imposed deadline, please refer to Appendix C of the draft decision.

The specifications for the study design

Premating exposure duration and dose-level setting

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

Ten weeks premating 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.[3]

[3] ECHA Guidance R.7a, Section R.7.6

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

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

Cohorts 1A and 1B

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

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

In your dossier, you have provided a justification for data waiving regarding "immunotoxic potential": *"A conclusion of "immunotoxic potential" is not warranted, since the blood cell observations were noted at doses where numerous signs of acute toxicity were also noted. In addition, other evidence suggests that recognized endpoints involving an immunological response, such as dermal sensitization, was negative. In general, immunotoxicity testing is not a standard requirement for Annex X substances (> 1000 t/a). Furthermore, the reduced WBC counts, the effects on spleen weights without a histopathological correlate and the increased platelet counts in the 90d inhalation study were observed in the mid and/or high dose groups (Landry et al., 1990). None of these findings were observed in the low dose group, resulting in the NOAEL of 300 ppm. Therefore, the observed blood cell and spleen effects are not relevant for the DNEL derivation and the overall risk assessment and thus, an additional immunotoxicity testing is not justified."*
However, ECHA notes that the repeated dose toxicity studies raise concern for developmental immunotoxicity. The dossier contains oral and inhalation repeated dose toxicity studies that are described below.

After the 14-day oral exposure in Sprague-Dawley rats ([redacted] 1991), the Substance showed reduced leucocyte and lymphocyte counts in females. Additionally, reduction in spleen weights were observed in both sexes at two highest doses with dose relation. Furthermore, reduction of thymus weigh was observed in females at mid and high dose level with dose relationship and in males at the highest dose. At the highest dose level, the thymus weight decrease was accompanied with thymic atrophy in both sexes. ECHA notes that the highest dose is 2000 mg/kg bw/day and therefore over the limit dose.

The 90-day inhalation study in Fisher 344 rats ([redacted] 1990) showed reduced WBC (females, dose relation) and lymphocyte count (males and females, dose-dependent) and statistically significant reduction in spleen weights in females. Therefore the findings support the concern regarding immunotoxic potential, seen in two different rat strains, with two different routes of exposure.

Furthermore, the USEPA HPV Challenge Program Submission document on 1,3-dioxolane [redacted] *by US-EPA*, 2009) states the following: *"After repeated dose or subchronic administration, effects on the blood forming systems, manifest as reduction in WBCs and platelets and changes in spleen weight appear to be the most sensitive target organs in rats."*

Existing information on the Substance itself derived from the available studies show evidence of immunotoxic potential, such as changes in haematology, histopathology and organ weights. These observations were seen also in absence of overt toxicity. In conclusion, there is an indication of immunotoxicity which needs to be investigated further.

In your comments to the draft decision, you address your concerns regarding doses to be selected for the EOGRT study. In specific, you note that: *"The Co-registrants are concerned that the doses to be selected for the EOGRT study, which are designed specifically to accommodate pre-mating, mating, and post-mating periods in a reproductive toxicity study, may be below doses that may produce potentialimmunotoxic effects."* Furthermore, you propose triggered approach to include Cohort 3 only if triggers are seen in immunotoxic sensitive endpoints during a dose range finding (DRF) study or in the parental generation in the OECD TG 443 study.

ECHA agrees that dose selection is critical for the optimal outcome of the study, as also specified under section *"Premating exposure duration and dose-level setting"* above. ECHA does not agree on the proposed approach for Cohort 3 as the triggers are already met and as the dose level setting must not compromise an appropriate investigation of the endpoint. Therefore, ECHA proposes to add an additional dose level for Cohort 3 to ensure a high enough dosing for immunotoxicological findings, as also recommended in ECHA Guidance R.7a, Section R.7.6.4.2.3. Furthermore, the study design needs to be scientifically justified and the existence or non-existence of the trigger(s) needs to be recorded.

Therefore, the developmental immunotoxicity Cohort 3 needs to be conducted.

Species and route selection

The study must be performed in rats with oral[4] administration. The volatile nature of the Substance has to be taken into account in selecting the route and method of administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B if relevant information becomes available from other studies or during the 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 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 ECHA Guidance[5].

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[5] ECHA Guidance R.7a, Section R.7.6.

Appendix B: 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[6].

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[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

The substance subject to the present decision was provisionally listed in the Community rolling action plan (CoRAP) for substance evaluation in 2016. The substance evaluation has been postponed until relevant data has been produced to address the concerns.

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 19 July 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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

Deadline to submit the requested information

The timeline indicated in the initial draft decision to provide the information requested was 24 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline to 36 months. Furthermore, you provided us with further documentation from the CRO to support the foreseen delay in performing the study due to laboratory capacity issues and to justify your deadline extension request. Therefore, ECHA modified the timeline to 36 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 D: List of references - ECHA Guidance[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] 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 E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.