ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 September 2017

Addressee: [redacted]

Decision number: CCH-D-2114372120-64-01/F
Substance name: 2-furaldehyde
EC number: 202-627-7
CAS number: 98-01-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21.07.2016
Registered tonnage band: 1-10T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. ***In vivo* mammalian erythrocyte micronucleus test (Annex X, Section 8.4., column 2; test method: OECD TG 474) in mice or rats, oral route with the registered substance; or *In vivo* mammalian bone marrow chromosomal aberration test (Annex X, Section 8.4., column 2; test method: OECD TG 475) in mice or rats, oral route with the registered substance; or *In vivo* mammalian alkaline comet assay (Annex X, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum, with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **5 October 2020**. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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

1. **In vivo mammalian erythrocyte micronucleus test (Annex X, Section 8.4., column 2), or *In vivo* mammalian bone marrow chromosomal aberration test (Annex X, Section 8.4., column 2; test method: OECD TG 475); or *In vivo* mammalian alkaline comet assay (Annex X, Section 8.4., column 2; test method: OECD TG 489)**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex X, Section 8.4. provides that "*If there is a positive result in any of the* in vitro *genotoxicity studies in Annexes VII or VIII, a second* in vivo *somatic cell test may be necessary, depending on the quality and relevance of all the available data.*"

The technical dossier contains several *in vitro* studies (chromosome aberrations) which were performed: according to OECD TG 473 (on CHO cells) for one and according to no specific guideline for the other three (on CHO and on V79 cells) with the registered substance. The four tests all show positive results. The positive results show that the substance is inducing chromosomal aberrations under the conditions of the tests.

The technical dossier also contains five *in vivo* studies, three of which are appropriate for addressing cytogenicity information and two of which are appropriate for gene mutation information. Of the cytogenicity studies, one is a Lethal mutation test (publication) using *Drosophila* and performed according to OECD TG 477 with the registered substance, showing positive and negative results; a second one is chromosome loss test in germ cells and wing spot test in somatic cells of *Drosophila melanogaster,* performed with the registered substance, not following any specific test guideline and showing positive results. The third *in vivo* study is similar to an OECD TG 475 test, in mice by intraperitoneal route, performed with the registered substance, and showing negative results.

ECHA considers that the first two tests are not appropriate to fulfil the requirements, as they were not performed on mammalian species allowing an assessment of their relevance for humans. You reported some deviations for the third *in vivo* test (only males, no data on the different types of chromosomal aberrations). However the main deficiency relates to the missing second sampling time, post single exposure as per paragraph 33 of OECD TG 475:

> "*Bone marrow samples should be taken at two separate times following single treatments. For rodents, the first sampling interval should be the time necessary to complete 1.5 normal cell cycle lengths (the latter being normally 12-18 hours following the treatment period). Since the time required for uptake and metabolism of the test chemical(s) as well as its effect on cell cycle kinetics can affect the optimum time for chromosomal aberration detection, a later sample collection 24 hours after the first sampling time is recommended.*

At the first sampling time, all dose groups should be treated and samples collected for analysis; however, at the later sampling time(s), only the highest dose needs to be administered. If dose regimens of more than one day are used based on scientific justification, one sampling time at up to approximately 1.5 normal cell cycle lengths after the final treatment should generally be used." (emphasis added).

ECHA concludes that the study has no 17+24-hour sample available to be assessed, and so does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), as required by Annex XI, 1.1.2.

Two further *in vivo* studies address gene mutation information, a DNA repair study (UDS) in rats and mice ([redacted] 2001) and a transgenic mutation assay in the mouse ([redacted] 2003) were also submitted. ECHA notes that these two studies are considered to be suitable to follow up *in vitro* positive results for gene mutation. By contrast ECHA considers that they are not suitable to follow up *in vitro* positive results for chromosomal aberration (cytogenicity).

In your comments on the draft decision, you have argued that you would not be subject to further information requirements, as *in vivo* somatic cell genotoxicity studies are available. ECHA accepts that your argument is correct. ECHA has amended the legal reference to Annex X, 8.4 and included the following reasoning: in your comments, you have argued that the study of [redacted] (1990) is valid, and that the missing second sampling time is not required. In respect of the argument that a second sampling time is not required in the OECD TG 475, you argue that (1) there is rapid metabolism/ excretion of furfural (2) furfural was detected as positive at an early sampling time *in vitro*, and therefore the negative at an early sampling time *in vivo* is definitive. ECHA notes that the OECD TG 475 does not identify these arguments as valid reasons to modify the sampling time requirements of the test. ECHA additionally considers that these are not adequate arguments for removing the second sampling time. In respect of (1), ECHA considers it is possible that furfural present in the body for the first 24 hours could cause an effect at later than 17 hours. In respect of (2), ECHA notes that *in vitro* kinetics of furfural, and cellular response, can differ from the *in vivo* response. Thus, *in vitro* results are not predictive in all respects of the *in vivo* response. Additionally, your comment is based upon scientific studies which are not provided in the comment or in the dossier. Consequently, ECHA is not able to evaluate these studies and the extent to which they support your arguments. Summarising, ECHA maintains that the *in vivo* study does not have adequate and reliable coverage of key parameters as a result of the missing sampling time.

You also indicated that "*the [registered] substance has been evaluated in accordance with the chemicals legislation preceding the REACH regulation. In particular, Council Regulation 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances identified the Substance as priority substances for evaluation. In the framework of this evaluation, the European Commission imposed testing and information requirements on the importers or manufacturers of certain priority substances, including the Substance. In February 2008, the* [redacted] *finalized the risk assessment for the Substance. During this risk assessment an* in vivo *gene mutation test was requested [...]. Within this review, the* [redacted] *competent authority reviewed the* in vivo *study* [redacted] *1990 and did not identify the mentioned deficiency.*

Therefore, the registrants of the Substance have the expectations that the review and risk assessment undertaken by a competent authority of a test in the past will not be challenged by another authority without any new facts or knowledge." The previous regulatory work carried out by the [redacted] authorities pursuant to Regulation (EEC) No 793/93 does not prevent ECHA to establish compliance of the information with the REACH information requirements, according to Article 41 REACH, especially because the registered substance has triggered member states' concern in relation to mutagenicity and carcinogenicity. Therefore you need to comply with the respective information requirements irrespective of the fact whether earlier regulatory work (carried out more than 10 years ago). Therefore, ECHA considers that your comment does not form the basis of a waiver.

In your comments, you also raised a concern about the use of the word "concern". ECHA reiterates that this process is a compliance check, and has clarified wording where appropriate to remove ambiguity. You have further argued that the proposal for the comet assay is excessive and inconsistent, and specifically the specification of tissues to be tested. ECHA has modified the wording of the decision to make clear that our decision is 'in line with' the Test Guideline. ECHA has already included here detailed legal and scientific considerations as to why, beside analysing the liver, testing additional tissues sample is recommended while performing the required test according to OECD TG 489.

In addition, you have proposed a read-across to furfuryl alcohol, mentioning a specific study [redacted], 2016 – conducted in compliance with OECD TG 489), and provided justifications has to how the read-across approach can be acceptable, in separate Annex. ECHA notes that the study referenced is not present in the registration dossier (submission [redacted], of 20 July 2016), nor is it provided in the comment. Therefore ECHA cannot perform any evaluation of this study. In addition, ECHA considers that the simple assertion that furfuryl alcohol is rapidly and extensively metabolised to furfural is not a sufficient basis for predicting the properties of the registered substance, according to Annex XI, Section 1.5. You would need to provide a detailed factual basis to support your proposition, to show that any systemically available furfuryl alcohol does not confound the prediction, to show that there are no differences in metabolism between the two substances, and to show that the metabolic conversion of furfuryl alcohol to furfural does not lead to different toxicological consequences, as compared to direct administration of furfural. These are currently not present in the body text, although there are two toxicokinetics reports in the dossier.

ECHA has also examined your read-across proposal in the Annex of your comments, and notes that it is principally based on the hypothesis that furfuryl alcohol is converted to furfural. ECHA notes that some of the studies cited in support of this hypothesis are not provided in the comment nor in the registration dossier, and so cannot currently be evaluated. On the basis of the information provided, ECHA considers that you have not demonstrated that furfuryl alcohol is rapidly (i.e. within 20 minutes) and extensively (i.e. >90%) metabolised to furfural, nor that any systemically available furfuryl alcohol does not confound the prediction, nor that there are no differences in metabolism between the two substances, nor that the metabolic conversion of furfuryl alcohol to furfural does not lead to different toxicological consequences, as compared to direct administration of furfural. Additionally, ECHA considers that (1) there is evidence of different toxicity of the two substances, e.g. acute and repeated- dose toxicity (2) there is an insufficient database to justify that the two substances have similar toxicity. In view of all these considerations, ECHA considers that there is not a reliable basis for predicting the properties of the registered substance from the read-across substance.

In conclusion, no appropriate *in vivo* genotoxicity study to follow up on the *in vitro* positive results assessing potential for chromosomal aberrations is available for the registered substance, although it is necessary to meet the legal information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the *ECHA Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.7.6.3, the mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) or the mammalian bone marrow chromosomal aberration test ("CA test", OECD TG 475) are suitable to follow-up a positive *in vitro* result on chromosomal aberration if the test substance or its metabolite(s) will reach the target tissue. Alternatively, the *in vivo* mammalian alkaline comet assay ("Comet Assay", OECD TG 489) is a suitable test to be performed.

In case you decide to perform a MN or CA assay according to the test method OECD TG 474/ OECD TG 475, the test shall be performed in mice or rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In case you decide to perform the comet assay according to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate. In line with the OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism (after oral administration, 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 sample both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

In vivo mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice or rats, oral route, or

In vivo mammalian bone marrow chromosomal aberration test (test method: OECD TG 475) in mice or rats, oral route, or

In vivo mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

Notes for your consideration

In case you decide to perform the comet assay, you may consider examining gonadal cells in addition to the other aforementioned tissues, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells.

However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. 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.

According to applicable test guidelines: *"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"* (paragraph 10 of the OECD TG 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) and paragraph 6 of the OECD TG 475 (Mammalian Bone Marrow Chromosomal Aberration Test, updated on 26 Sept 2014)).

Additionally, according to paragraph 48 (d) of the OECD TG 474 and paragraph 44 (d) of the OECD TG 475, a negative test result can be considered reliable if *"Bone marrow exposure to the test substance(s) occurred"*. Accordingly, if a substance is negative in this test, but it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material. However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt the information requirement for a pre-natal developmental toxicity study in a second species according to Annex X, Section 8.7.2., column 2. You provided the following justification for the adaptation *"the study does not need to be conducted because the substance is of low toxicological profile [...]"*. Column 2 states that [T]he studies need not be conducted if: ... *"the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2, because systemic effects were observed in repeated dose toxicity studies you have submitted (i.e. there is evidence of toxicity) and because you have not demonstrated that there is *no or no significant human exposure*. Indeed, you used, e.g. PROCs 8a, 8b, 15, to describe the uses at industrial sites (section 3.5.3 of IUCLID) and, e.g. PROCs 5, 8a, 11, to describe uses by professional workers (section 3.5.4 of IUCLID). Therefore, your adaptation of the information requirement is rejected.

In your comments you stated that "*An unpublished pre-natal developmental toxicity study has been referenced in the* [redacted] *dd. 2006. This study is expected to meet the information requirement of Annex X 8.7.2. in a second species. The registrants have no access to this full study.*" ECHA reminds you that according to Articles 10(a)(vii) and 13(5), robust study summaries "*shall be included in the technical dossier*" and registrants must be given "*permission to refer to the full study reports for the purpose of registration*". On the basis of the information provided in the comment, ECHA considers that there is insufficient information provided to enable an assessment of the validity of the study.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD TG 414, the rabbit is the preferred non-rodent species.

On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second species. However, if based on the available information and/or substance-specific properties the results from the rabbit would not be relevant for humans, you should justify and use a relevant different second species for testing.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (default rabbit) by the oral route.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex XI, Section 1.1. "study scientifically not necessary". You provided the following justification for the adaptation "*There are no fertility or reproduction studies available for furfural (2-furaldehyde). According to Annex XI Section 1.1.2: alternative relevant data for key parameters from studies with comparable exposure duration may be considered adequate for the purposes of classification and labelling and/or risk assessment. From the determination of estrus cyclicity (estrus stage and cycle length) and sperm analysis (testis weight, epididymis weight, sperm count and sperm motility) conducted as part of 14 week studies of repeat exposure to fufuryl alcohol by inhalation, there was no indication of any adverse effect in rats or in mice that would impair reproductive performance. These data for furfuryl alcohol are considered adequate for the purposes of classification and labelling and/or risk assessment of furfural. Very limited data available from studies of 13 week oral administration of furfural to rats and to mice did not indicate the potential for the chemical to adversely affect any of the reproductive organs and neither did the data obtained from the subsequent two year studies. However, it is recognised that the two year studies provide little relevant data for defining the potential effect of furfural on reproduction.*"

ECHA considers that you have provided a Weight of Evidence (Annex XI, 1.2) adaptation, using a 14-week study on a read-across substance, furfuryl alcohol, and also using 13-week and two-year studies on the registered substance.

In respect of the read-across to data on furfuryl alcohol, ECHA considers that this is a read-across according to Annex XI, 1.5. However, there is no documentation for the read-across. Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substance, furfuryl alcohol. In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance. Hence, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substance. Since your read-across does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected. Additionally, ECHA considers that there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3). Specifically, this test is missing a first filial generation, and all the associated analysis (fertility, gestation, offspring parameters).

In respect of the 13-week and two-year studies, ECHA notes that these also are missing the key parameters associated with reproduction, gestation and offspring parameters addressed in the corresponding test method referred to in Article 13(3).

Finally, you have not provided any explanation of how these studies altogether provide a sufficient weight of evidence for this endpoint. ECHA concludes that your adaptation does not provide sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion. The conditions of Annex XI, 1.2 are not met, and hence ECHA rejects your adaptation.

ECHA acknowledges your intention to improve the read-cross justification in order to demonstrate the possible prediction of relevant human health properties of the registered substance from data for the source substance. You have provided a read-across justification in an Annex of your comment. This justification relies upon some studies which are not available in the dossier or comment, and to that extent, ECHA cannot evaluate these studies or their relevance to the read-across justification. Your read-across hypothesis is primarily that furfuryl alcohol is rapidly and extensively metabolised to furfural, and so the properties of furfuryl alcohol can be read-across to furfural. ECHA notes (1) there is no quantitative information to confirm the statement "Furfuryl alcohol is "rapidly" and "extensively" oxidized to furfural"; specifically, this would involve quantitative information about systemic uptake and availability within hours after administration. It is not clear where the biotransformation occurs in the body, nor whether this would affect the toxicity of furfural. It has not been shown that there is no systemically available furfuryl alcohol, or that there are no differences in metabolism between the two substances. These considerations mean that the prediction of properties of the registered substance based on the properties of furfuryl alcohol, is not reliable. (2) The data matrix for toxicological properties already present data from read-across and not from the target/ source substances (e.g. for repeated dose toxicity by oral route, or developmental toxicity). There are (significant) differences in results between the target/ source substances for acute dermal toxicity and repeated dose toxicity by inhalation route. This information contradicts your read-across hypothesis. (3) ECHA notes that there is not any available study to be read-across for the EOGRTS endpoint, and so the read-across approach you propose would fail also for this endpoint. For all these reasons, the proposed read-across would fail to meet the requirements of Annex XI, section 1.5.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered.

According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should 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 because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some 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;

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3, if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

ECHA notes that the tonnage band for several members of the joint submission is 1 000 tonnes or more per year.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 04 November 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and amended 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 did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-55 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the *Community rolling action plan (CoRAP) for the start of substance evaluation in 2018.*

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

3. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.