ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 11 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453632-51-01/F
Substance name: Trimethoxy(methyl)silane
EC number: 214-685-0
CAS number: 1185-55-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/02/2018
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity)**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

You are additionally requested to perform:

3. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit or rat), oral route using the registered substance.**

You have to submit the requested information in an updated registration dossier by **18 June 2021**. You also have to update the chemical safety report, where relevant.

The reasons for 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

The decision of ECHA is based on the examination of the testing proposals submitted by you.

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (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 in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 443 inhalation route to be performed with the registered substance with the following justification:

"*In accordance with ECHA Draft Decision SEV-D-2114279311-53-01/D for this substance received on 29th April 2014, and notification from the Swedish Competent Authority in December 2015 that the data gaps for reproductive and developmental toxicity would be dropped from this draft decision and dealt with via a Compliance Check, the Registrants intend to conduct an extended one-generation reproductive study in the rat (OECD TG 443) via the inhaled route.*"

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA notes that you have submitted a testing proposal for the basic study design according to column 1 of Section 8.7.3., Annex X. ECHA considers that this basic study design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.
Premating exposure duration and dose-level setting

You proposed a basic study design.

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 if 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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

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 with the other cohorts being tested at the same dose levels.

In your comments on the draft decision, you consider that dose setting for the EOGRTS should not be driven by toxicity, but by toxicokinetic behavior if such information is available and indicates nonlinearity, and if the inflection point is well above human exposure levels. You also doubt the relevance of toxicity-driven dose selection because non-linear toxicokinetic behavior can well result in toxic effects that are of little relevance to human health under relevant exposure conditions. You consider that the results of this current requirement may lead to a risk of over-classification (with unnecessary regulatory implications and economic impact) and the suffering of additional animals.

ECHA notes that for REACH purposes, the study should be adequate for risk assessment as well as classification and labelling. To this end, the dose level selection should be based on toxicity. According to ECHA Guidance[5], "*The highest dose for an extended one-generation reproductive toxicity study should be selected with the aim to induce some toxicity (or to use the limit dose of 1000 mg/kg bw/day if humans are not exposed to higher dose levels), in order to allow a conclusion on whether effects on reproduction are considered to be secondary, non-specific consequence of other toxic effects seen [...]. Only in this way is it possible to assess if the substance is a reproductive toxicant and/or if the effects on reproduction are potentially associated with systemic toxicity and to what extent.*

The possibility to select the highest dose level, based on the toxicokinetic data as mentioned in EU B.56 (OECD TG 443) and in the OECD GD 151, may not allow comparison of adverse effects on fertility with systemic toxicity and, thus, does not support production of data for classification and labelling purposes, including categorisation. Regarding the highest dose level, it is important to ensure that toxicity in both female and male animals is considered to ensure that reproductive toxicity in either gender is not overlooked."

ECHA Guidance[5] highlights the use of dose range-finding studies and where information on

toxicokinetics may be helpful: "*Dose level selection is assisted by the information from existing studies as well as from specific dose range-finding studies that may need to be conducted. Toxicokinetic information may provide reasons to adjust for example, the dosing route and regime. In addition, it should be considered that toxicity and toxicokinetics in pregnant animals may differ to that in non-pregnant animals. This may cause challenges in selecting the highest dose level for the study as at various phases of the study the sensitivity of the animals may differ.*"
Finally ECHA notes that if there is no relevant data to be used for dose level setting, it is recommended that results from a 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.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by professionals (PROCs 10, 11, 19) and consumers as as adhesives and sealants, in coatings and paints, thinners, paints removers.

In addition, there are indications for endocrine-disrupting modes of action because of changes in reproductive organs and other endocrine organs (thyroid, adrenal glands in OECD 422, testes and epididymis in OECD TG 413 study).

In your comments on the draft decision, you stated that it is inappropriate to consider a potential ED mode of action based on the observations in OECD 422 (oral route) and OECD 413 (inhalation route) studies.

ECHA notes that endocrine disrupting modes of action may be indicated from *in vivo* studies e.g. by 1) changes in organ weight sensitive to endocrine disrupting activity (intact and/non-intact animals), 2) (increased) body weight, 3) measurements of hormone levels, or 4) effects on reproduction associated with endocrine (disrupting) modes of action. In the provided repeated dose toxicity studies (OECD 422 and OECD 413), changes in reproductive organs and other endocrine organs were observed. ECHA considers these findings as indications for endocrine-disrupting modes of action.

In your comments on the draft decision, you considered that adverse thyroid effects, i.e. thyroid gland follicular cell hyperplasia/hypertrophy, in OECD 422 study are secondary to liver enzyme induction and should not be considered as endocrine. However, ECHA considers that the observed thyroid effects in both genders are likely treatment-related relevant findings. Furthermore, a specific mehcanism for liver induction, for the registered substance, not relevant for human, was not demonstrated. As you have not provided any further evidence to support your consideration, the thyroid gland follicular cell hyperplasia/hypertrophy may not necessarily be secondary to any other toxicity observed.

In your comments, you also stated that thyroids were also collected for gross and histopathological examination in the 90-day inhalation study (OECD 413), but no test substance-related findings were observed. ECHA notes that these findings are not reported in the technical dossier. As no effects on the liver were observed in the OECD 413 study, you considered that this supports the view that thyroid effects observed in OECD 422 study via the oral route are secondary effects. However, this cannot be simply concluded due to

different routes of exposure, different strains of rats and different doses used in the two studies. As indicated above, the observations in repeated dose toxicity studies suggest that the oral route is more potent than the inhalation route. There can be route-specific differences in the toxicity pattern.

In addition to thyroid effects, ECHA considers the findings on the adrenal gland in the OECD 422 study, and on the testes and epididymes in the OECD 413 study as indications for possible endocrine-disrupting modes of action. According to your comments on the draft decision, the adrenal gland relative weight was only affected in male rats at a dose level of 250 mg/kg bw/day. You do not consider it to be treatment-related because it occurred only in males, and was apparent only in relative organ weight basis and had no corresponding microscopic findings. However, ECHA notes that effects of the registered substance on adrenal gland in male rats were not reported at all in the technical dossier. Therefore, ECHA has not considered this finding in the justification to request the extension of Cohort 1B. In the OECD 422 study, statistically significant histomorphological findings, including increase in adrenal gland follicular cell hyperplasia/hypertrophy (in 10/10 animals) and adrenal gland apoptosis (in 9/10 animals), were observed in female rats at the highest dose level (1000 mg/kg bw/day). In your comments on the draft decision, you considered that these findings are not test-substance related adverse effects as the histomorphology of the adrenal gland was not affected in the female recovery group or in male rats. ECHA acknowledges that the histomorphological changes, which were observed only in females in the adrenal gland, seem to be reversible in the screening study. ECHA, however, notes that the high incidence of adrenal gland follicular cell hyperplasia/hypertrophy and adrenal gland apoptosis at the highest dose level suggests that the findings are related to the test substance. Furthermore, effects like hyperplasia and apoptosis should usually be regarded as adverse.

ECHA notes also that in the OECD 413 study (inhalation), absolute adrenal weight increased in females at the two highest exposure levels, i.e. 18% (400 ppm) and 25% (1600 ppm). Additionally, an increase in relative adrenal weight was observed in females at the highest exposure level (27%). There was no histological correlate and the finding was not present in males or recovery group females. Nevertheless, ECHA considers that the effects observed in adrenal gland in female rats also via inhalation route further suggest that this endocrine organ could be a target for the registered substance.

The weights of testes and epididymides were decreased in the high exposure level (1600 ppm) recovery group male rats in the OECD 413 study (inhalation). In your comments on the draft decision, you stated that these findings correlated histologically with marked testicular seminiferous tubule degeneration and corresponding epididymal oligospermia. In the regular 90-day study, seminiferous tubule degeneration was observed only in one control and one low-exposure (25 ppm) rats. You considered that these effects are not related to the test substance, but are rather spontaneous findings in young Sprague Dawley (SD) rats. However, ECHA notes that in the technical dossier, it is stated that two recovery group males showed marked testicular seminiferous tubule degeneration and corresponding epididymal oligospermia (one unilateral, one bilateral). ECHA notes also that the recovery group consisted only of control and the high exposure group (1600 ppm) rats. Therefore, ECHA considers that possible testicular effects cannot be ruled out in the absence of further evidence. Furthermore, it may indicate a latency in the effects onset beyond the 90d of test duration. Hence, a concern for an ED mode of action still exists.

ECHA considers that the findings in OECD 422 and 413 studies fulfil the condition in Annex X (Section 8.7.3, column 2) that there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies to trigger the extension of Cohort 1B to include the F2 generation.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there are indications of one or more relevant modes of action related to endocrine disruption from the available studies (OECD TG 422, oral route by [redacted], 2005 and OECD TG 413 by [redacted], 2008).

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance itself derived from an available *in vivo* study provided in the technical dossier with the registered substance (OECD TG 422; [redacted], 2005) show evidence of thyroid effects. Histomorphological changes in the thyroid gland have been observed in both males and females in the mid and high dose groups. The thyroid effects with the registered substance are of concern for the developmental neurotoxicity.

Therefore, ECHA considers that the criteria to include Cohorts 2A and 2B are met.

In your comments on the draft decision, you disagreed with the request of Cohorts 2A and 2B (DNT) based on the thyroid effects. You stated in the comments that thyroid hyperplasia/hypertrophy observed in both male and female rats in the OECD 422 study are secondary effects due to liver metabolism induction and no thyroid toxicity has been demonstrated. Therefore, you considered that the observed thyroid effects cannot be regarded as a particular concern to trigger DNT cohorts. In your comments on the draft decision, you also stated "*It is well-known that the development of the nervous system can be adversely affected if there is a significant change in the blood concentration of these hormones. Increased thyroid follicular cell hypertrophy and hyperplasia may be due to TSH stimulation of the thyroid gland subsequent to perturbations in thyroid hormone levels. This has not been demonstrated in this study and non-ED related MoA can't be ruled out e.g. a stress response.*"

ECHA points out that an endocrine disruption-related mode of action cannot be ruled out either. ECHA considers that the thyroid gland follicular cell hyperplasia/hypertrophy in both genders is likely a treatment-related relevant finding. As you have not provided any further evidence to support your consideration, the thyroid gland follicular cell hyperplasia/hypertrophy may not be secondary to any other toxicity observed. Furthermore, a specific mechanism for liver induction, for the registered substance, not relevant for human, was not demonstrated. Thus, the (developmental) neurotoxicity concern exists.

In your comments on the draft decision, you stated that thyroids were collected for gross and histopathological examination in the 90-day inhalation study (OECD 413), but no test substance-related findings were observed. ECHA notes that this finding is not reported in the technical dossier. Furthermore, no effects on liver were observed in OECD 413 study. You considered that this supports the view that thyroid effects observed in OECD 422 study via the oral route are secondary effects. ECHA notes that this conclusion cannot be directly drawn due to different routes of exposure, different strains of rats and different doses used

in the two studies. In the draft decision, ECHA has pointed out that the observations in repeated dose toxicity studies suggest that the oral route is more potent than the inhalation route.

In the comments on the draft decision, you addressed the term "particular concern" and referred to the ECHA guidance as follows: "*The ECHA guidance, chapter R7a guidance says: A particular concern means that the concern should be specific to (developmental) neurotoxicity but also that the concern needs to reach a certain level of severity. Based on text in REACH Annex VIII, 8.6.1 for example, it can be understood that a particular concern may be indicated, such as by serious or severe effects.*" ECHA notes that in the same ECHA guidance, a general term of trigger is used. According to ECHA guidance, examples of substance specific findings, which may indicate a particular concern justifying inclusion of the DNT cohort and considered as triggers, are relevant changes in thyroid hormone levels or signs of thyroid toxicity indicating such changes. No information is available on the effects of the registered substance on thyroid hormone levels. ECHA, however, considers that the thyroid gland follicular cell hyperplasia/hypertrophy observed in male and female rats via the oral route at mid and high dose levels indicates a particular concern that triggers the inclusion of Cohorts 2A and 2B.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified study on the registered substance itself.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X. ECHA notes that existing information on the registered substance itself and on a substance structurally analogous to the registered substance, derived from available *in vivo* studies show evidence of substance-related effects on thymus.

In the OECD TG 422 oral study with the registered substance a statistically significant decrease in absolute thymus weight was observed in males at the mid dose (250 mg/kg bw/day) (-28%) and at the high dose (1000 mg/kg bw/day) (-35%).

In addition, the structurally similar substance dimethoxydimethylsilane (EC number 214-189-4) tested in a OECD TG 422 study exhibited similar effects in the thymus in males.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* studies on the registered substance itself and a substance structurally analogous to the registered substance.

Species and route selection

You proposed testing in rats. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the inhalation route. However, you did not provide any justification for choosing this exposure route. ECHA considers that the oral route is usually 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) Chapter R.7a, Section R.7.6.2.3.2. ECHA notes that the substance is not a gas. According to the reported uses in the CSR, i.e. coatings and sealants, the most relevant route of exposure is inhalation since the "*techniques used by both professionals and consumers...are intimate hand mixing (PROC19) to cover initial mixing of paint (typically <15 minutes exposure), application by brushing or rolling (PROC10), and for professionals occasionally non-industrial spraying (PROC11).*" However, ECHA notes that the maximum inhalation exposure is not very high (9.9 mg/m^3) and that the substance to be tested is a non-irritating liquid of medium volatility (3000 Pa).

The studies provided in the dossier seem to show route-specific toxicity after oral and inhalation exposure in particular in effect levels and severity observed. After oral administration, thyroid and adrenal histopathology were affected and thymus weight reduced, whereas inhalation exposure only reduced adrenal and thymus weights. In more details, target organs in the oral study were thymus (decreased weight at 250 mg/kg bw/d), thyroid (follicular cell hyperplasia/hypertrophy: males and females at 250 mg/kg bw/d), and adrenals (hyperplasia/hypertrophy, apoptosis and lymphocytic infiltration: zona reticularis in females at 1000 mg/kg bw/d). In the inhalation studies the target organs were the adrenal glands in females (absolute weights statistically increased at about 600 mg/kg bw/d), and thymus (decreased weight in the females at about 600 mg/kg bw/d). However, there are several uncertainties in the reported information, (e.g. thyroid info not reported for the inhalation 90-day) which also need to be considered when concluding on route specific effects.

It is noted that via oral route, the systemic effects (such as thymus and thyroid effects) were detected already at 250 mg/kg bw/d, i.e. with a lower dosing than via inhalation route. A lower effect level and required shorter exposure duration via the oral route suggests that oral route is more potent than the inhalation route. Therefore, taking all the arguments above into account, it is considered that testing via oral route is more appropriate and ECHA considers that the study should be performed by the oral route.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the inhalation route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing in the rat as a first species. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the inhalation route. However, you did not provide any justification for choosing this exposure route. As indicated under the request 1, ECHA considers that testing via oral route is more appropriate and ECHA considers that the study should be performed by the oral route.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

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

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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).

As outlined above under 2. ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species rat or rabbit, according to OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity

study in a second species (Annex X, Section 8.7.2.). Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed in a second species (rabbit or rats), depending on the species tested in the first pre-natal developmental toxicity study.

For the testing in the first species you proposed testing in rat by the inhalation route. However, you did not provide any justification for choosing this exposure route. Similar to requests 1 and 2, ECHA considers that oral route is more relevant to investigate the hazardous properties of the registered substance related to reproduction.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit or rat), oral route (test method: OECD TG 414).

Notes for your consideration

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 3 October 2016.

ECHA held a third party consultation for the testing proposals from 12 April 2017 until 29 May 2017. ECHA received information from third parties. This information, however, does not provide any scientifically valid information or studies and, therefore, cannot fulfil the information requirements concerned.

This decision does not take into account any updates after **24 September 2018**, 30 calendar days after the end of the commenting period.

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

Following the notification of a first draft decision sent to you on 7 August 2017 (communication number TPE-D-2114363771-46-01/D), ECHA noted that the draft decision did accidentally not consider the prior evaluation results concerning developmental immunotoxicity in the study design of the extended one-generation reproductive toxicity study (request 1 of the present decision). In order to provide you with the opportunity to comment on the amended draft, ECHA decided to re-start the decision-making process by sending a new draft decision for your comments.

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

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

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. 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 the Member States.

3. 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.