Helsinki, 13 September 2018

Addressee: [redacted]

Decision number: CCH-D-2114440074-60-01/F
Substance name: O,O,O-triphenyl phosphorothioate
EC number: 209-909-9
CAS number: 597-82-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/05/2016
Registered tonnage band: 100-1000

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 vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that both studies requested under 1. and 2. have negative results;**

4. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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 ***20 March 2020***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.
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

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple toxicological endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach for toxicological endpoints in general before the individual endpoints (sections Annex VII 8.4, Annex VIII 8.4, and Annex VIII 8.7 of the REACH Regulation).

Grouping and read-across approach for toxicological information

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Thus, physicochemical and degradation properties influence the human health

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

i. **Description of the grouping and read-across approach proposed by you**

You consider to achieve compliance with the REACH information requirements for the registered substance O,O,O-triphenyl phosphorothioate (EC 209-909-9; CAS 597-82-0) using data of a structurally similar UVCB substance mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8) (hereafter the 'source substance').

You have provided a read-across documentation as a separate attachment under section 13 of the IUCLID dossier.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group:

(1) Similar structure and common functional groups

You state that, the source chemical is an UVCB substance and that the target mono-constituent substance is a major constituent of this source substance. You also state that the other constituents of the source substance are closely related structures (*"The target substance, CAS 597-82-0 is O,O,O-triphenyl thiophosphate, the source substance, CAS 192268-65-8, is a mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives. The main difference being that the additional components of CAS 192268-65-8 carry one or more tert-butyl residues at the phenolic rings").* Therefore, you consider that the source and the target substances share structural similarities with common functional groups.

(2) Similar physico-chemical properties

You argue that the physico-chemical properties of the source substance are in good correlation with the data for the target chemical. You specifically highlighted that the water solubility was found to be in a comparable (low) range as it is the partition coefficient and concluded that this relationship gives rise to an expected comparable degree of bioavailability and a similar toxicological profile.

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

(3) Similar toxicological properties between the source and the target substance

You claim that the toxicological data available for both substances is in strong support of the proposed read across approach because both chemicals share very similar toxicological properties in all endpoints tested such as acute toxicity, irritation and genetic toxicity. Furthermore, the assessment of the available repeated dose toxicity studies revealed a low systemic toxicity with adaptive changes in the liver and NOAELs of a similar magnitude.

As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ii. ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

With regard to the proposed predictions ECHA has the following observations:

The substance characterisation of the source substance need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4), it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 2.1, May 2017) also for the source substance. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes. Currently the identity of the source substance (and its impurity profile) is not detailed in the registration dossier.

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity, similar physico-chemical and toxicological properties has not established why the prediction is reliable for the human health endpoints for which the read across is claimed. In addition, ECHA understands your assertion that the target substance is a major constituent of the source substance and that the other constituents of the source substance closely related structures.

ECHA however, notes that although you state that the 'major' constituent of the source substance is similar to the target substance, its concentration in the source substance is only [redacted]%.
ECHA furthermore considers that you have not explained the impact of the tert-butyl moeites and their position (o,p,m) in the constituents of the source substance on toxicokinetics and toxicological properties. Hence, it is not possible to conclude whether these moieties change the toxicokinetics profile of the substances and consequently the toxicological properties.
You claimed similar effects in the toxicological studies. However, ECHA notes that in the Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD TG 422) whith the target substance, besides the centrilobular hepatocellular hypertrophy which was observed with the source substance at comparable doses (100 and 200 mg/kg bw/d for the source substance and 125 mg/kg bw/d with the

target substance), several other effects were noted. These additional effects that were not observed in a similar type of study, at comparable doses with the source substance are:

- Histopathological changes in adrenal glands (hypertrophy of zona fasciculata cells of the adrenal cortex) and thyroid glands (hypertrophy of the follicular epithelial cells of the thyroid) in 25, 125,(and 500) mg/kg females, albeit the thyroid effects are known to occur in rats, especially in males, treated with high doses of xenobiotics, secondary to hepatic enzyme induction
- Hypertrophy of the mammary tissue in 125 mg/kg (and 500 mg/kg) males.
- Decrease in implantation sites per litter at 125 (and 500) mg/kg bw/d
- Decrease in the number of live pups per litter at 125 (and 500) mg/kg bw/d

In the screening study with the source substance there were no fertility effects up to the highest dose of 250 mg/kg bw/d. The NOAEL for reproductive and systemic effects in the screening sudy with the target substance was 25 mg/kg bw/d. The available toxicological data suggest that the target substance has a higher toxicity and induces a wider range of effects than the source substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Accordingly, the analogue approach is rejected.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

Finally, Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

ECHA notes that the specific considerations for the individual endpoints which result in a failure to meet the requirement of Annex XI, Section 1.5., and are set out under the endpoint concerned, see in the sections below (1 to 5).

iii. Conclusion on the read-across approach

The adaptation of the standard information requirements, namely *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.), *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.), and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.), in the technical dossier is based on the proposed read-across approach from the analogue substance, UVCB substance mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8). For the reasons as set out above, ECHA does not consider the read-across justification to be a reliable basis to predict

the properties of the registered substance.

ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data of the source substances. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation. An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for two Ames tests (OECD 471), one with the registered substance on two strains (S. typhimurium TA 98 and TA 100), the other one on the analogue substance mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8).

However, as explained above in Appendix 1, section 'Grouping and read-across approach for toxicological information' of this decision, your adaptation of the information requirement is rejected.

In addition, ECHA notes that in the supporting study performed with the registered substance has deficiencies: the strains TA 1535 and TA 1537 or TA 97 and E.coli were not tested, the documentation was limited and no information was given on data source of metabolic activation.

Therefore, your adaptation of the information requirement is rejected.
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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information

specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an In vitro Mammalian Chromosome Aberration Test (OECD TG 473 with the analogue substance mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8).

However, as explained above in Appendix 1, section 'Grouping and read-across approach for toxicological information' of this decision, your adaptation of the information requirement is rejected.

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.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

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 vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain appropriate study records for this endpoint. Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under [1] and [2] have negative results. ECHA set the deadline for provision of the information to allow for sequential testing

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation [by providing a study record for an In vitro Mammalian Cell Gene

Mutation Test (OECD TG 476) with the analogue substances mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8).

However, as explained above in Appendix 1, section 'Grouping and read-across approach for toxicological information' of this decision, your adaptation of the information requirement is rejected.

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.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

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 vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 1. and 2. have negative results.

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

Firstly you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Reproduction / Developmental Toxicity Screening Test (OECD TG 421) with the analogue substance mixture of triphenylthiophosphate and tertiary butylated phenyl derivatives (CAS 192268-65-8). However, as explained above in Appendix 1, section 'Grouping and read-across approach for toxicological information' of this decision, your adaptation of the information requirement is rejected.

Secondly, you provided a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422) with the registered substance, showing

reproductive effects such as a decrease in implantation sites per litter at 500 mg/kg be/d and most importantly at 125 mg/kg bw/d, a decrease in the number of live pups per litter at at 500 and 125 mg/kg bw/d and the hypertrophy of the mammary tissue in 125 mg/kg and 500 mg/kg males. The last effects in males were not reported in the endpoint study summary but they are described in the read-across justification for toxicological endpoints in the context of the screening study available with the registered substance. However, in the study endpoint you deemed this study as "not assignable" with a reliability 4 due to the following reasons "*Secondary source. Study summary submitted to US EPA in accordance with TSCA Section 8(e) without detailed information on test substance identity (no CAS number or CAS name given), methods employed or study results.*"

Thirdly, you provided a waiver for an extended one generation study with the following justification:

"*An extended 1-generation study is not performed at this point. The summary of a reproduction toxicity screening study of unknown reliability with test material of lesser quality is available showing decreased viability of offspring. At the same time, no reprotoxic effects were reported in an OECD 422 study performed with a test substance consisting of* [redacted] *% of CAS 597-82-0 next to* [redacted] *% of structurally close-related substances, thereby contradicting the previously described results. Based on the results of these two studies an uncertainty regarding reprotoxicity remains and further data would be beneficial for an accurate assessment. In order to clarify these remaining uncertainties, a proper OECD 421 study will be performed with the test article (high purity). In addition, a testing proposal for a subchronic toxicity study (OECD 408) is included in the dossier. These two studies will generate sufficient and reliable data to allow for a better assessment if an OECD 443 is required. If further testing is indicated after completion of the two studies, the OECD 421 study can directly serve as the required range finding study for the then necessary extended one-generation study. This step-wise approach will assure that animal lives are only spent when necessary.*"

However, ECHA notes that this adaptation does not meet any of the specific rules for adaptation set in Annex IX, Section 8.7.2., column 2 nor any of the general rules for adaptation set Annex XI. Furthermore, the studies used as argument for waiving are yet to be provided.

Therefore, your adaptation of the information requirement is rejected.

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.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, 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:
- Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement with the following justification for the adaptation:

"*A developmental toxicity study is currently performed with the read across substance (see chapter 13 for justification). Once completed, the study will be used to fill this data gap by a read across approach.*"

While you have not explicitly claimed an adaptation, your waver could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.5.

However, as explained above in Appendix 1, section 'Grouping and read-across approach for toxicological information' of this decision, your adaptation of the information requirement is rejected. Furthermore, the above mentioned developmental toxicity study is yet to be provided.

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.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, 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 first species (rat or rabbit) by the oral route.

Note for your consideration
ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

ECHA notes that the tonnage band for several members of the joint submission is 100 to 1 000 tonnes 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 03 April 2018.

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 did not receive any comments by the end of the commenting period.

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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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.