EUROPEAN CHEMICALS AGENCY

Helsinki, 19 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482449-35-01/F
Substance name: Triphenyl phosphite
EC number: 202-908-4
CAS number: 101-02-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/11/2018
Registered tonnage band: 100 to 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. **Composition of the substance (Annex VI, Section 2.3.);**
   - **Nature of impurities, including isomers and by-products**
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 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 **28 September 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.

The scope of this compliance check decision is limited to the standard information requirements of Annex VI, Section 2.3 and Annex IX, Section 8.7.2. of the REACH Regulation.

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, Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

The proposed read-across is discussed in section 0 of this decision because it is based on similar justifications. The corresponding section 2 (pre-natal developmental toxicity study in a first species) refers to the conclusion of section 0 while also analysing other information provided in the dossier and the need for further data to meet the relevant information requirements.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

Annex XI, 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

0.1 Your proposed read-across justification

In the registration dossier, you have provided a read-across justification for human health hazard assessment, using the source substances phenol (EC number 203-632-7; CAS number 108-95-2) and triphenyl phosphate (EC number 204-112-2; CAS number 115-86-6).

You have provided the following read-across studies to adapt the information requirements of Annex IX, Section 8.7.2. (pre-natal developmental toxicity study) by applying a read-across adaptation following REACH Annex XI, Section 1.5.:

- pre-natal developmental toxicity study using the source substance phenol (EU RAR, 2006);
- pre-natal developmental toxicity study in rats and mice using the source substance phenol ([redacted] 1983); and
- pre-natal developmental toxicity study using the source substance triphenyl phosphate ([redacted] 1987).

To justify the read-across, you stated that "*the metabolism of TPP has been described as involving step-wise hydrolysis of the parent phosphite with release of phenol, or oxidation of the parent compound to triphenyl phosphate with subsequent step-wise hydrolysis to release phenol ([redacted], 1992). Complete metabolism would result in the release of three molecules of phenol, and phosphoric acid. The hydrolysis rate of TPP is pH-dependent. Oxidation of TPP to the more stable phosphate form is the basis for its successful commercial use as an antioxidant. The relative bioavailability of the phosphite vs phosphate forms and their comparative hydrolysis kinetics have not been fully described. While there are no specific toxicokinetic studies of TPP, toxicology testing appears to indicate that it is readily absorbed via the oral route. Due to its rapid hydrolysis in water, it may be appropriate to consider the toxicokinetics of phenol for oral and inhalation routes since there would be a high likelihood of hydrolysis via these routes. The Phenol RAR (ECB 2006) concludes 100% absorption via the oral and inhalation routes and rapid elimination with low potential for bioaccumulation. These conclusions are also being applied to TPP.*"

On page 2 of the technical comments by [redacted] dated 17 August 2015 in IUCLID section 13 similar considerations with respect to the degradation pathway of triphenyl phosphite are made. On page 7, the hydrolysis and oxidation pathways of triphenyl phosphite is depicted.

ECHA understands that the basis for prediction of the proposed read-across is the hypothesis that triphenyl phosphite and its oxidation product triphenyl phosphate are rapidly hydrolysed to the common substance phenol and that phenol is representative for the toxicological properties of the registered substance triphenyl phosphite and its oxidation product triphenyl phosphate; *i.e.* the parent substance triphenyl phosphite and the possible other (bio)transformation products such as triphenyl phosphate, diphenyl phosphonic acid, diphenyl phosphite, diphenyl phosphate, phenyl phosphonic acid, phenyl phosphite, phenyl phosphate, phosphorus acid, phosphonic acid, phosphoric acid do not significantly influence the observed toxicity profile.

Although you did not explicitly explain why you provided the read-across studies using the source substance triphenyl phosphate, ECHA understands, that it was provided to support the assumption that there are no significant differences in toxicological properties between triphenyl phosphite, triphenyl phosphate and phenol with respect to reproductive and pre-natal developmental toxicity.

0.2 ECHA analysis of the grouping and read-across approach

With regard to the proposed prediction, ECHA has the following considerations:

(i) The substance characterisation of the source studies needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide "*How to report on Read-Across*" it is recommended to follow the Guidance on identification and naming of substances und REACH (version 1.3, February 2014) also for the source substances. 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.

ECHA notes that the source substance phenol is identified by its chemical name, CAS and EC number and the purity of the test material phenol is stated as 100% in [redacted] and 99.9% in the [redacted] ([redacted] 1983). The source substance triphenyl phosphate, however, is identified by its chemical name, CAS and EC number and its purity is given as 98% without further details on impurities ([redacted] 1987). Therefore, the impurity profile of the source substance triphenyl phosphate cannot be assessed using the information provided in the registration dossier and, hence, ECHA cannot verify the suitability of this substance for read-across. As the structural similarity between the source substance triphenyl phosphate and the target substance cannot be established on the basis of the available documentation, prediction of toxicological properties is not possible.

(ii) In order to meet the provisions in Annex XI, Section 1.5 to predict human health effects from data for a source substance, it has to be justified why such prediction is possible in view of identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

In the present case you explained that phenol is the final hydrolysis product of the step-wise hydrolysis of triphenyl phosphite and its oxidation product triphenyl phosphate. In this respect, the technical comments by [redacted] refer to [redacted], 1992. Although the referenced text by [redacted], 1992 has not been provided in the registration dossier, ECHA concludes that it is likely that phenol is formed from triphenyl phosphite and its oxidation product triphenyl phosphate by hydrolysis. However, you have not provided any evidence that this *step-wise hydrolysis* is the only (bio)transformation pathway acting on triphenyl phosphite or triphenyl phosphate; *i.e.* you have not addressed the question whether other (bio)transformation products are formed which might influence the prediction other than the hydrolytic pathway; i.e. you did not consider whether any of the intermediate hydrolysis products and the final hydrolysis product phenol undergo further (bio)transformation to other products (e.g. conjugation/ oxidation) which might influence the prediction. For example, you did not address the metabolic fate of the hydrolysis product phenol and how its metabolites could influence the prediction. In the hydrolysis report (attached to section 5.2.1. in IUCLID), you state that little or no accumulation of the possible di- and mono-ester hydrolysis products is expected, however, you have not provided any documented evidence to support this assumptions. In view of the rather long half-lives of 1.1 hours at pH 1.3, 0.5 hours at pH 6-7, and less than 14 hours at pH 9, ECHA considers that also the presence of intermediate hydrolysis products and their metabolic fate should be addressed.

You stated that the hydrolysis rate is pH-dependent and rapid. However, the half-life of the registered substance in aqueous hydrochloric acid (pH 1.3) is 1.1 hours at 25 °C according to [redacted] 1991 (see IUCLID dossier, section 5.1.2). Furthermore, the hydrolysis half-lives of the structural analogue triphenyl phosphate are 19 and 3 days in buffered solutions at pH 7 and pH 9, respectively, indicating a rather slow hydrolysis (see Material Safety Data Sheet of triphenyl phosphate).[2] Therefore, you have not shown that (bio)transformation of triphenyl phosphite and triphenyl phosphate to phenol is sufficiently rapid and complete to exclude systemic bioavailability and internal exposure to the parent compounds or any of the intermediate hydrolysis products. When considering that bioavailability of triphenyl phosphite, its oxidation product triphenyl phosphate or any of its intermediate hydrolysis products is likely due to the long half-life of 1.1 hours, it should be explained why systemic exposure to these substances would not significantly influence the toxicological properties under consideration. However, you have not included any such explanation. ECHA concludes that you did not address important aspects such as the toxicokinetics of the parent substance triphenyl phosphite and its oxidation product triphenyl phosphate and their metabolic fate and the resulting possible differences in their metabolite profiles. Therefore, it is not possible to verify that the source and target substances have the same, common mechanism of action which would allow predicting toxicological properties as a result of structural similarity in accordance with Annex XI, Section 1.5.

In absence of any data showing rapid hydrolysis to phenol, ECHA notes that the structural differences between triphenyl phosphite, its oxidation product triphenyl phosphate and phenol are significant: Whereas the phosphorus compounds are esters of phosphorus acid and phosphoric acid which exert differences in redox potential, phenol (aromatic alcohol) contains a free hydroxyl function which exerts a significantly different reactivity compared to esters of phosphorus and

[2] See https://us.vwr.com/store/asset?assetURI=https://us.vwr.com/stibo/hi_res/eng_us/96/21/8189621.pdf

phosphoric acid. E.g. phenol readily undergoes metabolic glucuronidation and sulfonation due to its nucleophilic properties whereas such reactivity is not observed for the parent ester compounds. You have not explained why these structural differences and their inherent different reactivity result in similar toxicological properties with respect to reproductive toxicity. Therefore, the provided explanation provides no basis for predicting the properties of triphenyl phosphite from triphenyl phosphate or phenol which does not rely upon conversion to phenol.

Finally and most importantly, existing toxicity data does not support your read across hypothesis. You have provided study records for repeated dose toxicity studies which show significant qualitative and quantitative differences with respect to toxicological effects: For triphenyl phosphite, a NOAEL(systemic, P) of 15 mg/kg/day based on lower body weight gain, ataxia, and foot splay was derived from the modified OECD 422 study using the registered substance ([redacted] 2004). For phenol, a NOAEL of 450 mg/kg bw/ day in rats and 370 mg/kg bw/day in mice based on reduced body weight gain was derived from carcinogenicity studies ([redacted] 1980); a NOAEL(maternal toxicity) of 140 mg/kg bw/day in mice (increased mortality, reduced body weight gain) and 120 mg/kg bw/day based in rats (reduced weight gain) was derived from pre-natal developmental toxicity studies ([redacted] 1983). For triphenyl phosphate, a NOAEL of 516 mg/kg bw/day based on significantly lower body weights was derived from the one-generation reproductive toxicity study ([redacted] 1987). According to the expert witness statement by [redacted] dose levels of 1000, 300, 200, 100, 50 and 40 mg/kg bw/day lead to "*unacceptable*" and "*excessive toxicity*".

In this respect, reference is also made to the Substance Evaluation Report for triphenyl phosphite which states that in a dose-range finding study "*in the mid-dose group of 300 mg/kg/d, 3/10 animals were killed moribund between study days 4 and 8*". Hence, if test animals would be exposed to triphenyl phosphite at the same dose levels used for the source substances phenol and triphenyl phosphate this would lead to excessive toxicity.

Furthermore, triphenyl phosphite displays "progressive toxicity" (i.e. worsening of effects with longer treatment) which seems to be absent in studies using phenol and triphenyl phosphate. Such significant differences in toxicological properties between target and source substances may indeed stem from qualitative differences (i.e. exposure to different substances) and/or quantitative differences (e.g. exposure of target tissues to different concentrations of a substance). The observed differences may actually indicate that triphenyl phosphite and/or any of its intermediate (bio)transformation products is systemically available and exerts different effects at lower exposure levels than phenol and triphenyl phosphate.

Therefore, ECHA concludes that the presented evidence contradicts your hypothesis that hydrolysis of triphenyl phosphite is sufficiently rapid, and on this basis also, it is not possible to predict the toxicological properties under consideration.

For the reasons set out above under (i) to ii), ECHA considers that the proposed adaptation does not meet the requirement of Annex XI, 1.5 that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

(iii) Additionally, Annex XI, Section 1.1.2 (2) and Annex XI, Section 1.5 require for non-GLP studies and studies used for read-across purposes that "*adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)*". Annex XI, Section 1.1.2 (2) and (3) and Annex XI, Section 1.5 require for non-GLP studies and studies used for read-across purposes "*reliable coverage*" and "*reliable documentation*".

0.3 Conclusions

The adaptation of the standard information requirement for pre-natal developmental toxicity (Annex IX, Section 8.7.2.) in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance from source substances phenol and triphenyl phosphate for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects the read-across adaptation in the technical dossier for pre-natal developmental toxicity.

1. Composition of the substance (Annex VI, Section 2.3.)

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

Annex VI, section 2.3. of the REACH Regulation requires that each registration dossier contains sufficient information for establishing the composition of the registered substance and therefore its identity.

In that respect, according to chapter 4.2 of the Guidance for identification and naming of substances under REACH and CLP (Version: 2.0, December 2016) – referred to as "the Guidance" thereinafter, you shall note that, for well-defined substances, the following applies:

- Each main constituent (i.e. the constituent present at ≥80% for mono-constituent substance or each constituent present at ≥10% and 80% for multi-constituent substance) shall be identified and reported individually; and

- Each impurity present at ≥1% or relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually.

- For each constituent, the typical, minimum and maximum concentration levels shall be specified regardless of the substance type.

In the present dossier, you identified the registered substance as a well-defined mono-constituent substance. You have reported the main constituent triphenylphosphite ([redacted]%, typically [redacted]%) and one impurity, phenol ([redacted]%, typically [redacted]%) in the legal entity composition provided in section 1.2 of your dossier. However, the chromatographic analysis included in section 1.4 ("[redacted]") reveals the presence of [redacted] other unidentified impurities, one of them being >1% according to the quantitation method provided. These impurities are not reported in the legal entity composition.

Furthermore, we note that the phenol impurity concentration ranges reported in your legal entity composition record ([redacted]% (w/w) are not coherent with the range reported in the boundary composition record ([redacted] % (w/w).

Therefore, ECHA concludes that the compositional information has not been provided to the required level of detail, because the impurities [redacted]% (w/w) were not identified and correctly reported in section 1.2

In your comments on the draft decision, you indicated that the compositional information will be reviewed and updated.

You are accordingly requested to correct the information provided on the composition of the registered substance, providing the typical and minimum concentration for the main constituent, identifying each impurity >1% (w/w) or relevant for the classification and/or PBT assessment and reporting such impurities with the typical, minimum and maximum concentration levels.

Regarding how to report the composition of the registered substance in IUCLID, the following applies: you shall report individually any impurity required to be identified and specify at least one of the following identifiers: chemical name, CAS number, EC number and/or molecular formula, as well as the minimum, maximum and typical concentration, in the appropriate fields in Section 1.2 of the IUCLID dossier. You shall ensure that the compositions reported in section 1.2 are consistent with each other and that the compositional information is completed up to 100%. The legal entity composition shall be verifiable and therefore supported by a description of the analytical methods for the identification and quantification of the constituents required to be reported, as required under Annex VI.2.3.7. of the REACH Regulation. The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

2. 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 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.

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.

In the technical dossier you have provided the following study records and an expert opinion

- [redacted](2004):a modified OECD TG 422 study in rat, oral route, using the registered substance
- EU RAR (2006): a read-across prenatal developmental toxicity study (OECD TG 414) using the source substance phenol (EC number 203-632-7) in rat, oral route
- [redacted] (1983): a read-across prenatal developmental toxicity study (OECD TG 414) using the source substance phenol (EC number 203-632-7) in mouse, oral route
- [redacted] (1983): a read-across prenatal developmental toxicity study (OECD TG 414) using the source substance phenol (EC number 203-632-7) in rat, oral route
- [redacted] (1987): a read-across prenatal developmental toxicity study (OECD TG 414)

using the source substance triphenyl phosphate (EC number 204-112-2) in rat, oral route
- An opinion provided by [redacted] (2015)

In addition, you have provided the following justification for the adaptation: "*According to Annex XI, Section 1.1.2, Data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3), and Section 1.5, Grouping of substances and read-across approach. Data shall: (1) be adequate for the purpose of classification and labelling and/or risk assessment; (2) be adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3); (3) have exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and (4) be adequate and reliable documentation of the study is provided. When considered against Annex XI Adaption Criteria, The existing reproductive and developmental toxicology dataset for TPP and its major biotransformation products: 1) is considered to be adequate for the purpose of classification and labelling and/or risk assessment; 2) provides adequate and reliable coverage of the key developmental toxicity parameters foreseen to be investigated in a prenatal developmental toxicity study; 3) employed exposure durations similar to those in the prenatal developmental toxicity study; and 4) has adequate and reliable study documentation available. Data provided on triphenyl phosphate and phenol are considered suitable for read across purposes. These substances are structurally relevant biotransformation products of the registered substance and as such are considered to represent the inherent properties of the registered substance. The existing dataset for TPP and its major biotransformation products are considered to provide sufficient weight of evidence, as defined in Annex XI, Section 1.2, to characterize the reproductive and developmental toxicity of the registered substance. Additional studies are therefore considered to be scientifically unjustified and not in the interests of animal welfare.*"

ECHA understands that the study records provided and supplemented with an expert opinion are meant to be used as adaptation justification under REACH according to Annex XI, Section 1.1.2. (use of existing data), Annex XI, Section 1.2. (weight of evidence), and Annex XI, Section 1.5. (read-across) and the provided information is evaluated against these adaptation rules.

ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 1.1.2. because the modified OECD TG 422 study by [redacted] 2004 does not adequately and reliably cover the key parameters of a pre-natal developmental toxicity study according to OECD TG 414 like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.
You have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a pre-natal developmental toxicity study using the source substance phenol (EU RAR, 2006); a pre-natal developmental toxicity study in rats and mice using the source substance phenol ([redacted] 1983); and a pre-natal developmental toxicity study using the source substance triphenyl phosphate ([redacted] 1987). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As set out above, ECHA concludes that neither the modified OECD TG 422 study by [redacted] (2004) nor the read-across prenatal developmental toxicity studies using either the source substance phenol (the hydrolysis product of the registered substance) or the source substance triphenyl phosphate (oxidation product of the registered substance) are sufficient to fulfil the information requirement according to Annex IX, Section 8.7.2.

The weight of evidence adaptation according to Annex XI, Section 1.2 requires several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property. According to your adaptation "*The existing dataset for TPP and its major biotransformation products are considered to provide sufficient weight of evidence, as defined in Annex XI, Section 1.2, to characterize the reproductive and developmental toxicity of the registered substance.*"

ECHA notes that this weight of evidence adaptation cannot be accepted because it does not explain why the read-across studies add sufficient weight as independent source of information to [redacted] (2004) leading to the conclusion that the registered substance has or has not a particular dangerous property with respect to prenatal developmental toxicity. Considering the significantly different toxicological properties of triphenyl phosphite and phenol, and triphenyl phosphite and triphenyl phosphate (in particular the significantly lower effect levels and progressive toxicity of the registered substance), and ECHA's rejection of the proposed read-across, ECHA is of the opinion that data on phenol and triphenyl phosphate is inadequate to support a weight of evidence approach for triphenyl phosphite for toxicological endpoints.

In section 13 of the IUCLID dossier, you provided an expert witness statements by [redacted] dated 18 August 2015 including considerations for the request of a pre-natal developmental toxicity study.

ECHA understands that this expert witness statement was filed during decision-making of the substance evaluation process for the registered substance triphenyl phosphite. ECHA takes this expert witness statement into account for this compliance check as it can be seen as an adaptation justification.

However, ECHA notes that the expert witness statement by [redacted] addresses general issues linked to approval of the animal study, duration of the study, and costs which are not substance specific and are not linked to any specific adaptation possibility according to column 2 of Section 8.7.3., Annex IX or any general adaptation possibility according to Annex XI of the REACH Regulation.

In your comments on the draft decision you explain that while the [redacted] (2004) study is not a standard PNDT study, it should be considered as fulfilling the standard information requirement according to Annex IX, 8.7.2. ECHA notes, however, that this study did not investigate foetuses at the appropriate age (i.e. caesarean section one day prior to the expected day of delivery) and at an appropriate level of detail (external, skeletal and visceral examination of all pups) as required by OECD TG 414. The [redacted](2004) study only investigates developmental effects of pups by gross necropsy after parturition (on PND 4 on culled F1 pups; at weaning on non-selected F1 pups; on PND 70 on retained F1 pups). This study therefore lacks essential investigations on PNDT such as delay in development as well as malformations and variations in foetuses of appropriate age. Therefore, the [redacted] (2004) study might have missed, for example, malformations in cannibalised pups, identification of dead foetuses present *in utero* (i.e. before parturition versus during parturition), delay in development and variations present at one day prior to the expected day of delivery.

Furthermore, you explain that the weight of evidence (WoE) and read-across (R-A) only relate to the reproductive toxicity information requirements and therefore ECHA cannot discount or disregard an adaptation on grounds which do not relate to the endpoints in question. ECHA fully understands that your WoE and R-A adaptations address the PNDT

information requirement. ECHA does not agree with you that the adaptation was rejected based on information irrelevant for reproductive toxicity.

ECHA agrees with you that information on the hydrolysis product phenol and the oxidation product triphenyl phosphate (TPPa) are relevant information also for the registered substance triphenyl phosphite (TPP). However, as explained herein, the provided information relating to phenol and TPPa are not sufficient to fulfil the PNDT information requirement or the WoE/R-A adaptation.

You are of the opinion that the (bio)transformation of TPPa and TPP in the available studies addresses the concern stemming from the (bio)transformation products of TPP. However, the available information does not evaluate PNDT of foetuses of the appropriate age for TPP and its metabolites, which contain a phosphite moiety.

You also explain that it is expected that TPP oxidises quickly to TPPa. However, ECHA notes that this expectation is not supported by evidence and therefore it cannot be concluded to what extent data from TPPa can be used to predict the toxicological properties of TPP.

You state that the R-A should not merely be rejected based on different toxicological properties of TPPa and phenol. ECHA notes however that the underlying R-A hypothesis is based on toxicological similarity between the registered substance, TPPa and phenol, which is not supported by the provided information as explained in this draft decision.

You explain further that data on TPPa and phenol demonstrate that reproductive and developmental toxicity are not expected to be a concern for this class of related chemistry and that the major metabolites TPPa and phenol show absence of developmental effects. However, this WoE is rejected because it does not address the absence of PNDT of foetuses of appropriate age for TPP and its other (bio)transformation products, which contain a phosphite moiety.

In your comments on the draft decision, you state that the rate of hydrolysis is sufficiently rapid ("minutes not hours"). However, results of the newly provided hydrolysis study on TPP ([redacted] 2017) in the updated registration dossier show that the hydrolysis of TPP is rather slow: Under acidic conditions (pH 4.09), the DT50 is 21.9 hours and under neutral conditions (pH 7.03, close to physiological pH), the DT50 is 14.7 hours. These results confirm ECHA's conclusion that it is very likely that the parent substance TPP including its (bio)transformation products containing a phosphite moiety are systemically available which contradicts your WoE and R-A justification.

You explain that it is unlikely that the toxicological effects worsen with time and that the observed worsening effects are rather related to higher dosing. ECHA notes however that from the full study report it is not clear if the effects indeed show worsening with time at the same dose level as the differences in effects might also stem from the different life stages (pre-mating, gestation, lactation).

You also state that the unknown impurities of TPP do not hinder the R-A. ECHA notes however that one of the fundamental requirements of R-A is structural similarity. Also impurities present at low percentage might have a considerable influence on the toxicological profile of a substance. Therefore, impurities need to be considered.

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 4.1, October 2015) R.7a, chapter 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.

Appendix 2: Procedural history

You were notified that the draft 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. However, following your comments on the draft decision and the inter-related new and substantial information provided in the updated dossier, ECHA has taken into account all the updated information relevant to the draft decision. Based on the average production and/or import volumes for the three preceding calendar years, the tonnage band has been changed from >1000 tonnes per year (submission number: [redacted]) to 100-1000 tonnes per year (Latest submission number: [redacted]).

The compliance check was initiated on 3 April 2017.

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 all the updated information of submission [redacted]. As a result, the following requests were removed:

- The request for classification and labelling was removed because you self-classified the registered substance as STOT RE 2 based on the study results of the OECD TG 422 study ([redacted] 2004).
- The requests for prenatal developmental toxicity study in a second species and extended one-generation reproductive toxicity study were removed because the highest tonnage band of the joint submission is 100-1000 tpa (Annex IX), and the existing information on the registered substance does not reveal triggers for these information requirements at Annex IX.

The deadline was amended accordingly.

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. The substance subject to the present decision is listed in the Community rolling action plan (CoRAP). A corresponding substance evaluation decision was issued on 21 May 2015 and appealed on 19 August 2015. During the appeal proceedings, the substance-evaluation decision was rectified by removing the request for a pre-natal developmental toxicity study and extended one-generation reproductive toxicity study from the decision (rectified decision was issued on 2 December 2015) and the remaining data gap for reproductive and pre-natal developmental toxicity has been addressed in this compliance-check decision.

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 in relation to Annexes VI to IX of the REACH Regulation, 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 compositions manufactured or imported by each registrant.

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