ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 11 May 2017

Addressee: [redacted]

Decision number: CCH-D-2114360752-49-01/F
Substance name: TETRAPHENYL M-PHENYLENE BIS(PHOSPHATE)
EC number: 260-830-6
CAS number: 57583-54-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28.05.2015
Registered tonnage band: 1000+T

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. **Name(s) in the IUPAC nomenclature or other international chemical name(s) (Annex VI, Section 2.1.1.) of the registered substance;**
   - **Chemical name**
   - **EC and/or CAS entry**
2. **Composition (Annex VI, Section 2.3.) of the registered substance;**
   - **Identity of the constituents**
3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance with inclusion of measurement of plasma, erythrocyte and brain cholinesterase activity;**
4. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat), oral route with the registered substance with inclusion of measurement of plasma, erythrocyte and brain cholinesterase activity;**

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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **20 May 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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 Kevin Pollard, Head of Unit, Evaluation E1

[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.

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Appendix 1: Reasons

1. Name or other identifier of the substance (Annex VI, Section 2.1.)

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

Annex VI, section 2.1 of the REACH Regulation requires that the registration dossier contains adequate and sufficient information to enable each substance to be identified. In that respect, according to chapter 4.2 of the "Guidance for identification and naming of substances under REACH and CLP" (Version: 1.4, June 2016) – referred to as "the SID Guidance" thereinafter, a multi-constituent substance should be named as a reaction mass of the main constituents of the substance, where the main constituents are those present at concentration generally ≥ 10% and < 80% (w/w). Deviations from this 80%-10% rule may be justified on a case-by-case basis, as indicated in the SID Guidance (page 33).

In the present dossier, you identified the substance as a multi-constituent substance, however you provided the following identifiers which are related to a mono-constituent substance:

- IUPAC name "tetraphenyl 1,3-phenylene bis(phosphate)"
- EC number 260-830-6
- CAS number 57583-54-7
- Other identifiers such as molecular formula, structural formula, etc.

According to the information given in IUCLID section 1.2, the substance has two constituents present at a concentration ≥ 10% and < 80% (w/w): "[redacted]" and "[redacted]". These two main constituents should contribute to the name of the registered substance. No justification has been provided to deviate from this naming rule.

You are accordingly requested to revise the chemical name assigned to the registered substance. The substance shall be named as "Reaction mass of [names of the main constituents]". It is recommended that the names of the constituents are presented in alphabetical order and they are separated by the conjunction "and". In principle, the names should be given in English language according to the IUPAC nomenclature rules. All information referring to a mono-constituent substance is requested to be adapted in order to refer to the multi-constituent substance and to identify the substance correctly. The EC identifier currently assigned to the registered substance (EC entry 260-830-6) does not correspond to the registered substance and shall be changed. However, for technical reasons, you shall not remove or modify this EC entry when submitting the updated dossier, as the registration is linked to that EC entry in REACH-IT. In addition, the current CAS identifier shall be removed.

Alternatively, you are requested to provide a justification for deviating from this naming rule in accordance with the SID Guidance.

Regarding how to enter the information in the IUCLID dossier, the following applies: you shall indicate, in the "Remarks" field of the reference substance in IUCLID section 1.1, the following: "The EC entry 260-830-6 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons". You shall also specify, in the same "Remarks" field, any available and appropriate EC number for the substance. In addition, you shall specify the chemical name as "Reaction mass of [names of the main constituents]" in the "IUPAC name" field and amend the molecular and structural information accordingly. Finally, you shall move the CAS information provided in the current submission to the "Related CAS information" field, and provide an appropriate CAS number for the substance, if available.

Further technical details on how to report the identifiers of multi-constituent substances in IUCLID are available in paragraphs 2.1 of the Data Submission Manual 18 on the ECHA website.

You should note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

However, pending the resolution of all the incompliances highlighted in the present decision, the adaptation of the identifier can only be effective once ECHA is at least in a position to establish unambiguously the identity of the substance intended by you to be covered with this registration. Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when the identifier adaptation process shall be initiated.

In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agreed to provide the requested information (revise the naming and the numerical identifiers) in a dossier update.

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

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

Annex VI, section 2.3 of the REACH Regulation requires that the registration dossier contains adequate and sufficient information to enable the composition of the substance to be identified. In that respect, according to the SID Guidance, when describing the composition of a multi-constituent substance the constituents present at ≥ 10% and < 80% (w/w) are considered as main constituents, and all the constituents which are not the main constituents are considered to be impurities (except additives). Furthermore each constituents shall be specified completely by all relevant parameters (e.g. chemical name and other identifiers, including the molecular and structural formula).

ECHA notes that you have listed all the constituents under the same constituents block, without distintion between main constituents and impurities.

Only constituents "[redacted]" and "[redacted]", appear to be present at a concentration ≥ 10% and < 80% (w/w) and are therefore to be considered main constituents. The remaining constituents appear to be at lower concentration and thus to be considered as impurities.

In addition, ECHA notes that the combined identification of the constituents (main and impurities) is not appropriate. More in detailed, all the constituents (except "[redacted]") were named "[redacted]" followed by a variable [redacted] to [redacted]. In addition, in the remark field of these constituents the following was reported "this is the n=X congener of RDP (p=Y)" (with X=[redacted] and Y=[redacted]). However, no explanation on the meaning of "n" and "p" was provided. Furthermore, such constituents were identified with the same molecular formula and molecular structure.

For this reason, the compositional information is not sufficiently clear to allow ECHA to verify the identity of the substance.

You are accordingly requested to modify the compositional information, according to the SID Guidance, and to provide complete chemical specification for each constituent present (the IUPAC name, EC number, EC name, CAS number and CAS name, molecular formulae and molecular structures) and correct identification of impurities.

Regarding how to enter the information in the IUCLID dossier, the following applies: you shall indicate, in IUCLID section 1.2 the constituents present at ≥ 10% and < 80% (w/w) as main constituents, and all the other constituents shall be reported under the impurities block. In addition you shall clearly identify all the constituents providing the IUPAC name in the "IUPAC name" field and if available any EC number, EC name, CAS number and CAS name. In addition you shall revise the molecular formulae and molecular structures in such a way that they correspond to the specific constituent they refer to.

Further technical details on how to report the composition of well-defined substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agreed to provide the requested information (revise the compositional information) in a dossier update.

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

ECHA notes that you have provided study summaries of the following studies performed with the registered substance: a sub-acute toxicity study (28-day) by the inhalation route, a sub-acute toxicity study (28-days) by the intraperitoneal route and a two-generation reproductive toxicity study by the oral route.

Firstly, you have sought to adapt the information requirement for a sub-chronic toxicity study (90-days) according to Annex XI, Section 1.5. of the REACH Regulation by indicating that an oral 90-day repeated dose toxicity study performed on the analogue substance Fyrolflex SOL-DP is ongoing. ECHA notes that the information on the sub-chronic study with the analogue substance – which was indicated in the dossier to be available in 2012 – is not provided in the dossier. In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you attached the report of the sub-chronic toxicity study performed with the analogue substance Fyrolflex Sol-DP and you indicated that you will update the dossier in due time.

With regard to your proposed read-across adaptation, ECHA notes that Annex XI, Section 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 a property-specific context.

(i) Information you provided on your read-across approach

You provided the below statement in the IUCLID endpoint study record 7.5.1. Repeated dose toxicity: *"According to Chapter R7a, section 7.5.4 of the 'Guidance on information requirements and chemical safety assessment', the potential toxicity of a substance, for which no data are available on specific endpoint, in some cases, can be evaluated by read-across from structurally or mechanically related substances for which experimental data exists. Fyrolflex RDP and Fyrolflex SOL-DP are two structural isomers which share similar toxicological profile (as described in details in attachment 1). Consequently, a read across between the two analogues can be performed. A 90-days oral toxicology study is currently performed on Fyrolflex SOL-DP. The results of this study will be read across to Fyrolflex RDP upon receipt of the final study report (year 2012). Hence, a 90-days oral toxicology study for Fyrolflex RDP can be avoided while animal welfare is respected."*

You have provided a read-across justification as a separate attachment in IUCLID, Section 7.5.1. "Read-across between Fyrolflex RDP and Fyrolflex SOL-DP". This justification document contains the following statement: *"The toxicological study results indicate very similar toxicological profile of the two analogue substances. Consequently, we believe that a read across between Fyrolflex SOL-DP and Fyrolflex RDP can be done based on experimental data and structural similarity. The difference in some of the phys-chem properties of the two isomers can be well understood by the difference in the degree of purity."*

(ii) ECHA analysis of your read-across approach

Structural similarity and dissimilarities and physico-chemical properties

You claim that:
"Structure comparison of these two isomers justifies performance of read-across, although, the appearance of two substances is different; Fyrolflex SOL-DP is solid at room temperature while Fyrolflex RDP is liquid. The difference in the physical appearance can be the result of the substance degree of purity. Fyrolflex SOL-DP is a mono constituent product while Fyrolflex RDP is a multi constituent product. This can also explain the difference in water solubility values of the two substances. Log Kow values are of the same order of magnitude."

ECHA notes that you have not addressed the obvious compositional (mono constituent versus multi constituent substance, respectively) and structural (*meta* isomer (resorcinol) and *para* isomer (hydroquinone), respectively) differences between the target and the source substance in context of the read-across hypothesis and did not explain why those differences would not lead to differences in the systemic toxicity profiles of target and source substance. The explanation provided is limited to the physical appearance of the substances, their degrees of purity and Log Kow, which do not address this concern. The compositional and structural differences might be one reason for the obvious toxicological differences observed in the repeated dose toxicity studies performed with the target and source substances (see below).

Support of a similar or regular pattern as a result of structural similarity

ECHA notes that in the dossier you indicated an ongoing sub-chronic toxicity study (90-day repeated dose toxicity) with the source substance Fyrolflex SOL-DP and you anticipated receipt of the final study report in the year 2012. However, the study has not been made available in the dossier under evaluation submitted in May 2015. In order to make an assessment of the proposed read-across with respect to repeated dose toxicity, the toxicological data generated with the source substance must be compared and discussed in relation to the substance under evaluation (target substance) in order to understand the similarities and differences of the toxicological profiles of the target and source substances.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you attached the report of the sub-chronic toxicity study performed with the analogue substance Fyrolflex Sol-DP. Based on that ECHA observes that in the sub-chronic study with the analogue substance Fyrolflex Sol-DP, doses up to 1000 mg/kg bw/day were well tolerated without indications of significant toxicity. However, the toxicological studies performed with the registered substance showed effects at lower doses. More specifically, slight increase of liver weight was observed at 145 mg/kg bw/day (sub-acute inhalation toxicity study, 28-day), at 50 mg/kg bw/day (sub-acute intraperitoneal toxicity study, 28-day) and at 49 mg/kg bw/day (two-generation reproductive toxicity study).

Hence, ECHA considers that there are obvious toxicological differences between target and source substance that do not support the proposed read-across approach.

Toxicokinetics

ECHA notes that in the read-across justification document you did not address the toxicokinetic properties of the target and source substance, their metabolic fate / (bio)tranformation and the resulting possible difference in the metabolite profile as part of the read-across considerations. ECHA notes that toxicokinetic differences may impact the toxicity of the substances and thus affect the possibility to predict the properties of the registered substance (target) from the data of the analogue substance (source).

In your comment(s) on the draft decision you acknowledge lack of relevant information on toxicokinetics of the source substance.

(iii) ECHA's conclusion on your read-across and grouping approach

ECHA concludes that in view of the issues listed above the source and target substance do not have the same properties or follow a similar pattern of toxicity and therefore does not allow prediction of the target (registered) substance toxicity.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirement for the endpoint sub-chronic toxicity study (90-day) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and is therefore rejected.

Secondly, you have further sought to adapt this information requirement. While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence.

(i) Information you provided on a weight of evidence adaptation

You have provided the following justification for the adaptation in the IUCLID endpoint study record stating the following:

"Conducting a 90-day repeated dose toxicity study with Fyrolflex RDP will not produce new information regarding the toxicity of the substance. After exposure of males and female rats for at least 16-17 weeks in a 2-generation oral reproductive toxicity study, a slight increase of liver weight was observed at 49 mg/kg bw/day. Similarly slight liver weight increases were observed after 28 days of treatment in an inhalation study at 145 mg/kg bw/day and in an intraperitoneal study at 50 mg/kg bw/day. In both 28-day studies, an equal inhibition was measured of the activity of plasma cholinesterase, an enzyme with no toxicological relevance for human risk assessment.

In conclusion, liver weight was shown to be the most sensitive effect parameter for exposure to Fyrolflex RDP. The LOAEL for a slight increase in liver weight was 145 mg/kg bw/day in the 4-weeks inhalation study and 49 mg/kg bw/day in the 2-generation study (at least 16-17 weeks of exposure). In view of the equivalent absorption of Fyrolflex RDP via the oral and inhalation routes of exposure, a LOAEL in between these two values is predicted for a 13-weeks toxicity study. In view of the 5-fold difference between the NOAEL and the LOAEL in the 28-day inhalation toxicity study (0.5 versus 0.1 mg/L), it is justified to predict a NOAEL of 16 mg/kg bw/day for a 90-day oral toxicity study, one third of the LOAEL in the 2-generation reproductive toxicity test."

Furthermore, you attached a justification document [redacted] in the dossier discussing the study designs and the respective results of the provided 28-day repeated dose toxicity studies and the 2-generation reproductive toxicity study.

ECHA notes that you have provided study summaries for two sub-acute toxicity studies and a two-generation reproductive toxicity study performed with the registered substance.

(ii) ECHA's analysis of the weight of evidence adaptation

ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and has assessed whether you have provided *"sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property"* with respect to the information requirement of Annex IX, Section 8.6.2. for sub-chronic toxicity according to OECD TG 408.

ECHA has further evaluated the information according to ECHA Guidance R.4.4. by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated the statistical power and whether the provided information is consistent and covers the relevant key parameters of a sub-chronic toxicity study (EU B.26./OECD TG 408).

Individual elements of the weight of evidence adaptation

ECHA notes that in the provided sub-acute toxicity studies the type of investigations are comparable to those of a sub-chronic toxicity study. However, the major differences are the exposure duration (28 days versus 90 days) and the lower number of animals used (5 per sex and dose versus 10 per sex and dose). Hence, sub-acute toxicity studies may not identify all effects that could be identified in a sub-chronic toxicity study.

ECHA notes that the provided two-generation reproductive toxicity study covers some parameters of a sub-chronic toxicity study (following 90-day exposure); e.g., histopathological evaluation of reproductive organs. ECHA further notes that in the provided study liver, brain, stomach and pituitary have obviously been weighed and examined for gross lesions, but not for histopathological lesions. For the other organs which are required to be examined in a sub-chronic toxicity study according to OECD TG 408, no information is provided. Hence, the provided information does not address all parameters of a sub-chronic toxicity study.

Furthermore, ECHA notes that the substance led to inhibition of plasma cholinesterase activity in the sub-acute toxicity studies. No inhibition was observed for erythrocyte cholinesterase activity; brain cholinesterase activity was apparently not measured. You indicated that the plasma cholinesterase was an enzyme with no toxicological relevance for human risk assessment implying that there was no relevant effect to human health. However, in the absence of measurements of brain cholinesterase activity and in the absence of measurements of plasma, erythrocyte and brain cholinesterase inhibition following sub-chronic exposure such a conclusion is not sufficiently robust.

ECHA also notes your extrapolation of a NOAEL for sub-chronic toxicity. However, such a calculation cannot appropriately address the NOAEL derived from an appropriate sub-chronic toxicity study and therefore such a calculation is not supported by any legal provision.

ECHA further notes that the deficiencies of individual pieces of evidence are not addressed in or covered by other pieces of evidence.

In summary, the evidence provided, either separately or jointly, does not allow to assume/conclude that the substance does not have a particular dangerous property, i.e., sub-chronic toxicity as investigated in a study according to OECD TG 408.

You conclude that "*Conducting a 90-day repeated dose toxicity study with Fyrolflex RDP will not produce new information regarding the toxicity of the substance.*"

However, ECHA notes that given the deficiencies explained above such a conclusion is not adequate.

(iii) ECHA's conclusion on the weight of evidence adaptation

In summary, ECHA considers that you did not provide an adequate justification for the proposed weight of evidence adaptation and that the evidence provided does not, in any case, allow to assume/conclude that the substance does or does not have the particular dangerous property sub-chronic toxicity as investigated in the standard test protocol of a study according to OECD TG 408.

Therefore, the conditions of Annex XI, Section 1.2. are not met and 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 has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Furthermore, ECHA notes that the sub-acute (28-day) repeated dose toxicity studies showed inhibition of plasma cholinesterase activity and no inhibition of erythrocyte cholinesterase activity. Hence, it is required to investigate plasma and erythrocyte choline esterase activity following sub-chronic exposure. In addition, ECHA notes that in the provided pre-natal developmental toxicity study with rabbits, cephalic malformations were observed. Even if such malformations did not reach statistical significance, they can be considered as a concern which might be due to inhibition of brain cholinesterase activity. Hence, ECHA consider it also necessary to investigate brain cholinesterase activity. Therefore, the clinical chemistry shall include investigations of plasma, erythrocyte and brain cholinesterase activity.
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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats with inclusion of measurement of plasma, erythrocyte and brain cholinesterase activity.

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

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

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

The technical dossier contains information on a pre-natal developmental toxicity study in rabbits by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement by providing the following justification for the adaptation *"A test for a developmental toxicity study in a second species can be waived according to Column 2 of Annex VIII of 1907/2006/EC as a pre-natal developmental toxicity study in rabbits (similar to OECD 414) and a two-generation reproduction study in rats (similar to OECD416) are available, in which no effects on development or reproduction were observed."*

ECHA notes that your proposed adaptation following Annex VIII, Section 8.7.1., column 2 applies only to the standard information requirement of Annex VIII, Section 8.7.1. and is not applicable to the standard information requirement of Annex X, Section 8.7.2.

Therefore, ECHA considers further whether your provided information may be seen as an attempt to adapt the information requirement following REACH Annex XI, Section 1.2., weight of evidence, and has evaluated your adaptation against those rules.

Annex XI, Section 1.2 requires that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, i.e. effects on pre-natal developmental toxicity in a second species.

ECHA has further evaluated the information according to ECHA Guidance R.4.4. by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated the statistical power and whether the provided information is consistent and covers the relevant key parameters of a pre-natal developmental toxicity study jn a second species (EU B.26./OECD TG 414).

(i) Information you provided on a weight of evidence adaptation

ECHA understands that you have provided information on pre-natal developmental toxicity on one species (rabbit) and information on peri-and post-natal developmental toxicity on a second species (rat). You are adapting the information requirement for pre-natal developmental toxicity in a second species (rat) based on "*no effects on development or reproduction*".

(ii) ECHA's analysis of the weight of evidence adaptation

The prenatal developmental toxicity study in the rabbit provides adequate information on prenatal developmental toxicity in first species. However, a two-generation reproductive toxicity study conducted in rats does not specifically address the (prenatal) developmental toxicity; only effects observable peri- and postnatally can be addressed affecting e.g. litter size, growth, and peri- and postnatal death. No investigations for possible incidences of external, visceral and skeletal malformation are performed in a two-generation reproductive toxicity study. Furthermore, due to cannibalism, malformations in pups cannot be usually observed. Thus, information on prenatal developmental toxicity in second species is very limited and indirect by nature.

In addition, ECHA notes that the pre-natal developmental toxicity study in rabbits as well as the two-generation reproductive toxicity study in rats showed indications for potential effects which needs to be investigated further. More specifically, in the pre-natal developmental toxicity study in rabbits, cephalic malformations were observed in one foetus each at the low and medium dose groups and in three foetuses at the highest dose group. Even if no statistical significance of those malformations were reached due to small numbers, they may be relevant and substance-related. The substance inhibits plasma cholinesterase activity and may inhibit also brain cholinesterase activity. However, brain cholinesterase levels were not measured. Inhibition of brain cholinesterase activity may affect the developing brain of foetuses and offspring and may be the mode of action for the cephalic malformations observed. ECHA notes that even if specific investigation in adult rats did not show neurotoxic effects, this does not exclude effects on the developing brain which might react more sensitively.

ECHA further notes that in the provided two-generation reproductive toxicity study, you concluded that "*No treatment related adverse effects were observed in P, F1 or F2 (no necropsy performed). Effects that were seen were related to flavor aversion to the test substance in food, resulting in a decrease in food consumption and alterations in body and organ weights.*" However, ECHA observes that for example, food consumption was not reduced in adult P1 dams during 10 weeks pre-mating period at any dose group, and in P1 males only at the high dose group and only at week 1. Food consumption was reduced in lactating dams only on lactation day 21 but not on lactation days 7 or 14.

This may indicate that exposed offspring, who consume the provided feed during end of lactation period, had lower body weights and consumed less food. Hence, ECHA cannot follow your conclusion that reduced food consumption and reduced body weights observed on offspring are due to flavour aversion. Those results more likely indicate substance-specific effect on development and it cannot be excluded that they may be linked to brain development. ECHA notes that no functional observations or neurological investigations were performed within this study.

These different pieces of evidence, taken together, do not support your assumption that the substance does not have effects on developmental or reproduction because these pieces of evidence have some deficiencies mentioned above and there are indications that the substance may lead to developmental effects that need to be further investigated.

Thus, your justification is not providing sufficient weight of evidence leading to the assumption/conclusion that the registered substance has no (prenatal) developmental toxicity, and you adaptation is not accepted.

In addition to the insufficient information on prenatal developmental toxicity on second species to support the adaptation, ECHA considers that the findings of the provided prenatal developmental toxicity study in rabbits and the two-generation reproductive toxicity study together with the concern related to the mode of action require further investigations.

Therefore, your adaptation of the information requirement for a pre-natal developmental toxicity study in a second species (rat) 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.

The test in the first species was carried out by using a non-rodent species (rabbit). According to the test method EU B.31./OECD 414, the rat is the preferred rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rat as a second 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 liquid, ECHA concludes that testing should be performed by the oral route.

Furthermore, ECHA notes that the sub-acute (28-day) repeated dose toxicity studies showed inhibition of plasma cholinesterase activity and no inhibition of erythrocyte cholinesterase activity. In addition, ECHA notes that in the provided pre-natal developmental toxicity study with rabbits, cephalic malformations were observed. Even if such malformations did not reach statistical significance, they can be considered as a concern which might be due to inhibition of brain cholinesterase activity.

Hence, ECHA consider it also necessary to investigate brain cholinesterase activity in addition to plasma and erythrocyte cholinesterase activity. Therefore, the clinical chemistry shall include investigations of plasma, erythrocyte and brain cholinesterase activity.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you indicated that you have "no comments" with regard to the requested information.

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

Appendix 2: Procedural history

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 26 May 2016.

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

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

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

ECHA referred the draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.