EUROPEAN CHEMICALS AGENCY

Helsinki, 27 September 2019

Addressee: [redacted]

Decision number: TPE-D-2114483966-28-01/F ]
Substance name: Zinc bis[bis(tetrapropylenephenyl)] bis(hydrogen dithiophosphate)
EC number: 234-277-6
CAS number: 11059-65-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06/03/2019
Registered tonnage band: 100-1000

## DECISION ON A TESTING PROPOSAL

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

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) and Pre-natal developmental toxicity study (OECD TG 414) using the analogue substance phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (EC no 270-608-0) is rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance;**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

The testing material used for performing the required studies shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

You are required to submit the requested information in an updated registration dossier by **4 April 2022**. You shall also update the chemical safety report, where relevant. The deadline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and specifications regarding the testing material are provided in Appendix 3.

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. of the REACH Regulation. The results of the Sub-chronic toxicity study (90-day) will be used, among other relevant information, to decide on the study design of the Extended one generation reproductive toxicity study. Therefore, your testing proposal for Extended one-generation reproductive toxicity study will be addressed after having received the results of the Sub-chronic toxicity study (90-day).

## 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 Ofelia Bercaru, 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 decision of ECHA is based on the examination of the testing proposals submitted by you, for the registered substance Zinc bis[bis(tetrapropylenephenyl)] bis(hydrogen dithiophosphate) (CAS No: 11059-65-7, EC No: 234-277-6, hereafter referred to as "target substance" or "registered substance").

In relation to the testing proposals subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirements for:

- Repeated-dose oral toxicity study (Annex IX, Section 8.6.2)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In IUCLID, Sections 7.5.1 and 7.8.2, you propose to test the analogue substance phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (CAS No 68457-79-4, EC no 270-608-0; hereafter referred to as "source substance" or "analogue substance") for the above mentioned information requirements. You propose to use the results obtained to adapt the standard information requirements for your registered substance by using a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation, as originally proposed for the "ZDDP category".

ECHA notes that in the updated dossiers of other substances in ZDDP category the testing strategy was changed, most importantly the new grouping excludes your registered substance.
In your updated dossier (submission number [redacted] you have aknowledged that the new grouping and read across approach exclude your registered substance, however you have not changed your testing strategy of using the above mentioned source substance to fulfil the information requirements using the grouping and read across approach.

ECHA has considered first the scientific and regulatory validity of your proposed grouping and read-across approach in general, before addressing the individual endpoints (sections 1 and 2).

### Grouping of substances and read-across approach

*Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis*

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by you are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

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

The first Recital and the first Article of the REACH Regulation establish the "*promotion of*

*alternative methods for assessment of hazards of substances"* as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to the present decision by using the results of the proposed tests is plausible based on the information currently available.

*General considerations*

For adaptations relying on 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 physico-chemical, toxicological and ecotoxicological 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 or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ecotoxicological 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 the 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 physico-chemical 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. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as lead to transformation products that may be hazardous, bioaccumulative and/or persistent. Thus, physico-chemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physico-chemical 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:
(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.

## A. Structural similarity and Grouping

The prerequisite for predictions based on read-across is the grouping of substances based on structural similarity. All substances in the proposed ZDDP category are complex reaction products with unknown or variable composition (Unknown or Variable composition, Complex reaction products and Biological substances: UVCB).

The characterisation of the substances identified as members of a category needs to be as detailed as possible in order to confirm category membership and to assess whether the attempted predictions are not compromised by the composition and/or impurities. The information provided on the substance characterisation of the category members must establish a clear picture of the chemical structures of the constituents of the members of the category. It is recommended to follow the *ECHA Guidance for identification and naming of substances under REACH and CLP*.[2]

For complex reported compositions with several constituents, structural similarity needs to be established taking into account all of the constituents of the substances. In the ECHA publication "Read-Across Assessment Framework (RAAF) – considerations on multi-constituent substances and UVCBs" (ECHA, March 2017) this is analysed in detail. The conclusion of this analysis is that for UVCBs grouping based on structural similarity becomes complex due to the presences of several or many constituents, higher variations in the concentrations of the constituents and unknown constituents. The presence of "pools[3]" of constituents further complicates the grouping explanations. In particular, for compositions with reported constituents, which are also UVCBs, extensive explanations have to be provided and justified criteria for group membership need to be established so that the group may form a reliable basis for predictions.

In the ECHA Guidance[4] the reporting format for a chemical category is described. The applicability domain of the category must be described by a "*set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members. Clearly indicate the borders of the category and for which chemicals the category does not hold. For example, the range of log Kow values or carbon chain lengths over which the category is applicable".*

### A.1 Your description of the structural similarities and the grouping

In your registration dossier, you have provided the following documentation as separate attachments in IUCLID Section 13:

- [redacted] (hereafter "justification document"). The document contains an overview of the grouping approach proposed, structural details (Appendix 2), data matrices with the physico-chemical properties (Appendix 3), and the toxicological properties (Appendix 4) of the category members.

[redacted]

[2] ECHA, May 2017, version 2.1
[3] The term "pool" is used to describe constituents with the same core structure, but different attached funtional groups. The term "pool" is used to avoid confusion with the term "group", which is used in Annex XI, Section 1.5, to describe a group of substances, whereas here pools of constituents are in focus. See also: Read-Across Assessment Framework (RAAF) – considerations on multi-constituent substances and UVCBs, ECHA, March 2017
[4] Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals, ECHA May 2008

[redacted]

Hereafter, ECHA refers to the two testing proposal documents as "testing strategy". Both documents present identical arguments and propose identical substance(s) to be tested.

You provide the following reasons for grouping the substances in the ZDDP category: "*The category of substances consists of a zinc atom with two dithiophosphate esters, surrounded by alkylated side chains (ZDDP). The alkyl ester substituent groups are saturated hydrocarbon chains that vary in length and extent of branching. Typically, the substances are prepared by* [redacted]

You consider that there is compositional similarity between the substances in the category due to the fact that the substances consist of three major constituent "groups" to which you refer to as "neutral ZDDP complexes", "basic ZDDP complexes" and "base oils".

You state: "*To serve different commercial intentions, and give different antiwear properties, an alkyl alcohol may be primary alkyl, branched chain primary alkyl, secondary alkyl, tertiary, and mixed depending on the ratio in the starting materials. ZDDP complexes exist in reversible monomeric or dimeric forms and a basic form. With regard to the basic form, it can convert to the neutral form and ZnO at elevated temperatures during intended use in a combustion engine.*"

Furthermore, you state: "*The substances in this category contain highly refined mineral base oil. The substances contain various base oils (10 EC numbers are identified), and as identified by the EC number there may be 1 to 6 different base oils added to the ZDDP substance.*"

This is further explained: "*ZDDP substances are manufactured and distributed in commerce in* [redacted]

And: "*In the category, the average percentage of added base oil was in the range of* [redacted] *and the mean for the category was* [redacted] *Thirteen of the category members have an average base oil content of less than* [redacted] *one category member has an average of* [redacted] *and two members have an average of* [redacted]

You have specified 15 substances as members of the category and you have placed these substances into two subcategories, alkyl ZDDPs (13 substances) and aryl ZDDPs (2 substances; grey shade in the table below). These substances, together with the EC identifiers and CAS numbers as reported, are presented in the table below. ECHA notes that the identifiers and names do not reflect the UVCB composition of the substances.

| EC number | CAS number | EC name |
|---|---|---|
| 230-257-6 | 6990-43-8 | Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate) |
| 270-608-0 | 68457-79-4 | Phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts |
| 283-392-8 | 84605-29-8 | Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts |
| 272-238-5 | 68784-31-6 | Phosphorodithioic acid, mixed O,O-bis(sec-Bu and 1,3-dimethylbutyl) esters, zinc salts |
| 272-723-1 | 68909-93-3 | Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts |
| 288-917-4 | 85940-28-9 | Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Bu and iso-Pr) esters, zinc salts |
| 270-478-5 | 68442-22-8 | Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Bu) esters, zinc salts |
| 218-679-9 | 2215-35-2 | Zinc O,O,O',O'-tetrakis(1,3-dimethylbutyl) bis(phosphorodithioate) |
| 247-810-2 | 26566-95-0 | Zinc bis[O-(2-ethylhexyl)] bis[O-(isobutyl)] bis(dithiophosphate) |
| 298-577-9 | 93819-94-4 | Zinc bis[O-(6-methylheptyl)] bis[O-(sec-butyl)] bis(dithiophosphate) |
| 273-527-9 | 68988-45-4 | Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Bu and pentyl) esters, zinc salts |
| 224-235-5 | 4259-15-8 | Zinc bis[O,O-bis(2-ethylhexyl)] bis(dithiophosphate) |
| 249-109-7 | 28629-66-5 | Zinc bis(O,O-diisooctyl) bis(dithiophosphate) |
| 259-048-8 | 54261-67-5 | Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) |
| 234-277-6 | 11059-65-7 | Zinc bis[bis(tetrapropylenephenyl)] bis(hydrogen dithiophosphate) |

Table 1: Substances specified as members of the ZDDP category; grey shade: aryl esters

The category members are ordered according to increasing molecular weight (top -> down) of the neutral ZDDP constituents. For the calculation of the molecular weight equimolar distributions of esters was assumed by you in case more than one alcohol is used to produce the esters. The molecular weight ranges from [redacted] for the alkylesters and is [redacted]

As support for your category grouping, you state that the physico-chemical properties of the category members are liquids with a low pour point, decompose at around 200 °C, give similar results when density and surface tension are investigated, are not flammable liquids, and are predicted to be non-explosive and non-oxidising on the basis of chemical structure.

You consider also that the substances generally exhibit limited water solubility, low vapour pressure and high viscosity. The range of experimentally determined water solubility values is from 5 to 2764 mg/L, and the range of measured LogKow is from 0.56 to 3.59.

Furthermore, you consider that the structural similarity for alkylesters (subcategory 1) is supported by Toxmatch results (Tanimoto index) that you present in a figure format.

### A.2 ECHA's analysis of the structural similarity and the grouping

You use the terms "neutral ZDDP complexes", "basic ZDDP complexes" and "base oils" to refer to the three major constituent "groups". As explained above ECHA prefers the term "pool[4]" to describe constituents with the same core structure, but different funtional groups. Therefore ECHA uses in this decision for the constituents the following terms:

- neutral ZDDP pool;
- basic ZDDP pool;
- the term "base oils" remains unchanged.

The neutral and basic ZDDP pools have variable phosphate esters. These esters are represented by the generic acronyms R1 and R2 (R3 is also possible for two substances). If the esters present in the ZDDP pools have e.g. [redacted] the neutral ZDDP pool is named in this decision [redacted] or the basic ZDDP pool is named in this decision [redacted]

The base oils are refined crude oils, and are considered by ECHA as individual UVCB substances.

ECHA notes that you state that the neutral ZDDP pool may reversibly form dimers; you do not describe the conditions, which lead to dimers, so it is not clear to ECHA whether dimers are usually present in your substances or not. For two substances dimers are reported in their compositions

ECHA understands that the basis for your grouping of substances in the ZDDP category is your claim of structural similarity due to the common presence of a zinc atom with two dithiophosphate dialkyl/diaryl esters and compositional similarity due to the presence of the neutral and basic ZDDP constituent pools, and base oils in the registered substances. You have attempted to support your grouping by physico-chemical properties and QSAR information, but the data provided contradicts or do not support your claims. In particular:

- The measured water solubility varies between 5 and 2764 mg/L and the measured octanol-water partition coefficients (log Kow) vary between 0.56 and 3.59. These ranges are very broad and many structurally very different organic chemicals fall in these ranges. Such broad ranges indicate likely differences in hazard properties and do not support your proposed grouping.

- You fail to document your assessment in the QSAR model reporting and prediction reporting formats (QMRF, QPRF). You do not provide the encoded chemical structures for the input to computational tools. It is unclear to what structures any estimations could be attached. The provided QSAR information therefore does not support your grouping.

Moreover, apart from the structural and compositional similarities there are also various dissimilarities between the substances, both structural and compositional, as presented

below. You do not consider what impact those dissimilarities have on the proposed grouping and the applicability domain.

Structural dissimilarities

ECHA observes the following sources of structural dissimilarities for constituent pools present in the composition of the members of the category:

- Neutral ZDDP pools:
  - The alkyl alcohols used to produce the esters of the phosphonates may be primary alkyl, branched chain primary alkyl, secondary alkyl, tertiary, and mixed depending on the ratio in the starting materials. This means the R1 and R2 in the structures may results from one alcohol only or from more than one in variable proportions. The alcohols range from C3 to C8 and may be branched at one or more positions or maybe linear.
  - Neutral ZDDP pools resulting from two alcohols in the reaction mixture contain a statistical mixture of combinations of the two alcohols. ECHA notes that alcohols used in the reaction may be UVCB substances themselves, e.g. phenol, dodecyl-, branched or feedstock sec-butanol 85 wt%, iso-octanol (mixed isomers). In such cases, entities will comprise a mixture of numerous isomeric forms resulting from the feedstock alcohol. Entities with chiral alcohols will comprise a mixture of the diastereomers.
  - Two aryl esters are included as a subcategory. These are obviously very different in structure and composition in comparison to the alkyl esters (presence of a p-substituted aryl-function and of tetrapropylenephenyl as constituent leading to Repro 1 B classification).
  - [redacted] ECHA notes that for [redacted]

- Basic ZDDP pools:
  - The same dissimilarities in terms of ester functions as for the neutral ZDDP pools exist for the basic ZDDP pools. The possible dissimilarities are multiplied by the 6 dialkyl dithiophosphates coordinated with 4 zinc atoms present in the basic ZDDP structure. Each of these dialkyl dithiophosphates may have a different statistical mixture of combinations of the two alcohols present for a given alcohol mixture. Due to this variability, the basic ZDDP are UVCBs, if more than one alcohol is present in the manufacturing process or if the alcohol is a UVCB.

- Base oils:
  - Different base oils were reported as possible constituents in the compositions of the substances in the ZDDP category. The base oils are UVCBs and their compositions are not reported. For some registered substances, several base oils are reported as constituents.

You did not take into account the relevance of the different ester functions for the grouping (e.g. [redacted] The fact that the aryl ZDDP pools are structurally obviously very different from the alkyl ZDDP pools demonstrate that the boundaries and the applicability domain of the category are not defined. You did also not support your claim that the different base oils present in the compositions do not affect the grouping and prediction possibility. ECHA

considers that you have not justified why these dissimilarities do not impact the grouping and would not compromise the attempted prediction of the relevant properties of the target substance(s) within the category.

Compositional dissimilarities
The concentration ranges for the ZDDP constituent pools and the base oils reported in the IUCLID section 1.2 for the compositions of the individual registered substances show that the compositions vary broadly. You did not take into account the relevance of the variations in constituent concentrations leading e.g. to [redacted] neutral ZDDP in one substance and to [redacted] neutral ZDDP in another substance of the category. The presence of [redacted] is reported for two substances, but not for the others. Or the basic ZDDP pools may be present e.g. at [redacted] in one substance and at [redacted] in another substance. Different base oils may be present or not. ECHA considers that you have not justified why these dissimilarities do not impact the grouping and would not compromise the attempted prediction of the relevant properties of the target substances within the category.

Applicability domain
You specified the substances to be included in the ZDDP category without inclusion/exclusion criteria. In particular, you did not provide any criteria for the inclusion/exclusion of esters formed from primary, secondary or tertiary alcohols, their chain length, their branching, or their UVCB nature. You did not provide criteria for the allowed variations of constituents in the compositions and you did also not provide criteria to define which base oils are allowed in the compositions of the group members. ECHA considers that under these circumstances the applicability domain is not defined.

### A.3 Conclusion on strucural similarities and the grouping.

ECHA concludes that the level of information provided on the composition of the different category members and the substance subject to this decision are not adequate to establish the similarity. There are structural and compositional dissimilarities which you did not take into account and which prevents the grouping as you proposed. The fact that the aryl ZDDP substances are included demonstrate that the boundaries of the category are not specified. As a consequence, the applicability domain of the category is ill defined and does not support predictions.

## B. Predictions

### B.1. Your category hypothesis and supporting information

You have provided documentation as described under A.1. above.

Your read-across hypothesis is that all the category members are "*structurally similar ZDDP complexes* [...] *when ordered by average molecular weight, each category member shows a sufficiently similar physico-chemical, toxicological, ecotoxicological and environmental fate profile to support read-across between the substances".* You further state that "[..] *the nature of the alkyl substituent groups (primary, secondary, mixed, or aryl), and the ratio of neutral to basic ZDDP [...]"* as well as *"[...] the presence of mineral base oil, at various levels"* would not significantly impact the toxicological properties of the substances.

You consider the RAAF[5] Scenario 6 (different compounds have the same type of effect(s)) to be the most relevant to this category approach because the read-across is based on "*the absence of systemic effects for all members of the category and no relevant variations in the strength of effects are predicted for the target substances in terms of the endpoints subject to a testing proposal*". You claim that the RAAF assessment elements for scenario 6 are satisfactorily addressed.

You use the following assumptions to support your hypothesis:

- *"All of the substances have local irritancy properties*
- *All of the substances have low acute oral toxicity (LD50 >2000 mg/kg)*
- *All of the substances have low acute dermal toxicity (LD50 >2000 mg/kg)*
- *All of the substances are non-sensitisers*
- *All of the substances are non-genotoxins*
- *All of the substances have a vapour pressure below ~0.01 Pa at 25°C*
- *Experimental Log Kow values are in the range of 0.6 to 4.0 with a mean value of 2.2*
- *Experimental water solubility values are in the range of 9.1 to 2764 mg/L, with a mean value of 1070 mg/L*
- *All of the substances are predicted to have zero or near zero absorbance via the oral route and consequently that systemic exposure will be trivial or non-existent"*

ECHA understands that your hypothesis is based on a claim of zero or near zero absorption via skin or gastrointestinal tract and the subsequent lack of systemic toxicity for the substances in ZDDP category. You provided the following considerations regarding toxicokinetic properties and the results of toxicity tests.

Toxicokinetic properties

No experimental data are provided, and you make the following assumptions:

- You consider a molecular weight above 500 as cut-off value for absorption
- You state that absorption is influenced by water solubility and lipophilicity
- You provide predictions obtained with SwissADME for absorptions

Results of toxicity studies

- You interpret the results obtained in acute and repeated dose toxicity studies as indication of lacking absorption.
- You have provided data matrices showing the available physico-chemical and toxicological data for the members of ZDDP category, including acute toxicity, skin/eye irritation, skin sensitization and genotoxicity.
- Further, you provided the following information on repeated dose toxicity:

  (i) Screening for reproduction/developmental toxicity study in rats, oral-gavage, at doses: 0, 10, 40, 160 mg/kg bw/day (OECD TG 422, GLP compliant; 2010). The test material is described as "Phosphorodithioic Acid, Mixed O,O-Bis(Iso-Bu and Pentyl) Esters, Zinc Salts /68457-79-4 / 270-608-0". You flagged this study as "key study". Your assigned reliability score is 1.

  (ii) Short-term (28-day) repeated dose toxicity study in rats, oral-gavage, at doses: 0, 10, 50, 125, 250, 500 mg/kg bw/day (equivalent to OECD TG 407, GLP compliant, [redacted] 1994). The test material is described as "1-Hexanol, 2-ethyl-, O,O-diester with phosphorodithioic acid, zinc salt / 4259-15-8 / 224-235-

[5] RAAF, https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

5". You flagged this study as "key study". Your assigned reliability score is 1.

(iii) Screening for reproduction/developmental toxicity study in rats, oral-gavage, at doses: 0, 30, 100, 200 mg/kg bw/day. (OECD TG 421, GLP compliant; 1995). The test material is described as "1-Hexanol, 2-ethyl-, O,O-diester with phosphorodithioic acid, zinc salt / 4259-15-8 / 224-235-5". You flagged this study as "key study". Your assigned reliability score is 1.

(iv) Short-term (28-day) dietary study in rats, nominal concentrations in diet: 1000 ppm (83.2 mg/kg bw M/93.0 mg/kg bw F), 2500 ppm (214.1 mg/kg bw M/233.8 mg/kg bw F), 7500 ppm (594.7 mg/kg bw M/678.5 mg/kg bw F) and 10,000 ppm (772.2 mg/kg bw M/861.9 mg/kg bw F) (equivalent to OECD TG 407, GLP compliant, [redacted] 1986). The study is reported for Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate) (230-257-6), however, the test material in the study is given only by trade name. Your assigned reliability score is 3 (*"test material composition unclear, impurity profile not specified, therefore unsufficient for assessment"*).

Selection of the source substance to be tested

In your testing strategy you justify the selection of the source substance (i.e. Phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (270-608-0) as representative for other substances in ZDDP category. You state that the substance is *"representative for the category as a whole"* and give the following criteria for selection: *"considered to be the worst-case in terms of potential for absorption", "includes a reasonable level of mineral base oil" and "has existing repeat dose data, albeit via the gavage route".*

You propose to test this source substance in a repeated dose oral toxicity study and pre-natal development toxicity study to fulfil the standard information requirements of Annex IX, Section 8.6.2. and 8.7.2. for the substance subject to this decision and all other substances in the ZDDP category.
Also, you have an intention to test the source substance in an 'enhanced' 21-day range-finding study *"to determine if the prediction of very low absorbance and no systemic exposure are valid"*.

In addition, in your testing strategy document, two additional substances are identified as possible future test substances (Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate) (230-257-6) and Zinc bis[O,O-bis(2-ethylhexyl)] bis(dithiophosphate) (224-235-5)). However, you have not identified them as test substances in IUCLID. These future plans are not considered in detail in the current testing proposal examination.

## B.2. ECHA analysis of your predictions of toxicological properties in light of the requirements of Annex XI, Section 1.5.

In the following, ECHA examines whether your hypothesis holds i.e. whether the substances in the ZDDP category have indeed *"zero or near zero absorption"* and whether they are likely to show no systemic toxicity or follow a regular pattern in their properties. Thereby, ECHA determines whether testing the source substance allows prediction for the relevant toxicological properties of the substances in the ZDDP category, including the substance subject to the present decision.

Based on this analysis ECHA concludes that you did not demonstrate the relevance of the proposed studies performed on the source substance (or on two extra source substances considered for possible future testing) for other substances in the ZDDP category, including the substance subject to the present decision. ECHA considers that you did not provide evidence that the selected source substance is *"representative for the category as a whole"* or is indeed a worst case for absorption. The reasons for this conclusions are specified below.

*B.2.1. Toxicokinetics*

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of substances in a category. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism and the determination whether the substances, which govern the systemic toxicity profiles are known and considered in the predictions.

With regard to toxicokinetic information, ECHA notes that you do not report any experimental data. Your statements on toxicokinetic properties are therefore based on theoretical considerations. Apart from that, it is not clear whether such considerations take into account the neutral and/or basic ZDDP constituent pools which are present in the composition of the ZDDP substances. Also for the base oils, toxicokinetic information is not provided. Additionally, predictions obtained with SwissADME are not valid, as the input structures for SwissADME in terms of constituent pools are not provided and there is no adequate documentation of method and results.

Absorption
ECHA has the following observations with regard to your claims on absorption.

Firstly, molecular weight is an important parameter influencing absorption. Although increasing molecular weights in general indicate that the likelihood of absorption decreases, the molecular weight differences between the individual neutral ZDDP pools cannot be used to predict differences in absorption for the substances with certainty.

Secondly, absorption is a process influenced by other parameters. Two of these parameters are water solubility and lipophilicity (Kow). As indicated in section A.2 above these parameters have a wide range of values across the category substances. Such great differences indicate differences in toxicokinetic properties and the likely consequence is that there are differences in the toxicological properties of the substances.

Thirdly, the potential for absorption of the parent constituents may be changed in the gastrointestinal tract resulting in hydrolysis/degradation products. You did not take into account the possible degradation products of the constituents in your consideration on absorption and the likely consequence on the toxicological properties of the substances.

Fourthly, ECHA notes that your hypothesis of no absorption is contradicted by your own statements in the registration dossiers of substances of ZDDP category. In particular, you state in IUCLID sections 7.1:

- For Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (230-257-6): *"The dermal adsorption is predicted to be moderate (50%), which is supported by the systemic*

*effects observed in the acute dermal toxicity studies. Intestinal adsorption is regarded to be effective as also supported by the existing acute oral toxicity studies."*

- For Phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (270-608-0): *"absorption by the GI tract is expected, and mostly by simple diffusion".*
- *For* Zinc bis[O,O-bis(2-ethylhexyl)] bis(dithiophosphate) (224-235-5): *"Taken together, EC# 224-235-5 absorption by the GI tract is expected, and mostly by simple diffusion."*
- For Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (272-732-1): *"Taken together, EC# 272-723-1 absorption by the GI tract is expected, and mostly by simple diffusion. EC# 272-723-1 may be transported through the circulatory system. This substance could potentially traverse cellular barriers and distribute to distant organs other than site of exposures. This argument is supported by (i) necropsy observations of lung, heart and gastrointestinal abnormalities, and loss of body fat and muscle in the acute dermal study; (ii) in the OECD 422 study, morbundity and adverse clinical effects were observed in rats treated with 160 mg/kg/d of EC 272-723-1, that suggested the test substances were bioavailable in rats."*
- For Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (249-109-7): *"Absorption via GI tract and skin is possible, inhalation is irrelevant".*
- For Zinc bis[bis(tetrapropylenephenyl)] bis(hydrogen dithiophosphate) (234-277-6 ): *Absorption in GI-Tract is relevant, dermal absorption is very low, and inhalation irrelevant.*

ECHA therefore considers that your hypothesis *"zero or near zero absorption"* is not supported and in fact it is contradicted by the information provided in the registration dossiers for substances of ZDDP category.

Consequently, ECHA considers that absorption via gastrointestinal tract and skin is likely for the constituents of the ZDDP substances. Also, absorption when the substances are inhaled cannot be excluded, as you have not provided reasons why absorption via inhalation is irrelevant for ZDDP substances, and since spray applications (PROC 7 and 11) are reported for some substances.

Metabolism

You have not discussed the influence of metabolism and the resulting metabolites on the toxicity of the ZDDP constituents in the justification document. However, in sections 7.1 of the IUCLID files possible metabolism pathways are identified, such as hydroxylation, oxidation, Zn-S reduction, oxidative desulfuration and ester hydrolysis.

Taking into account the possible metabolism pathways, the resulting metabolic products will be different for the different neutral and basic R1/R2 ZDDP pools and also for the different base oils. You do not identify the possible metabolites formed via the above mentioned pathway and the resulting toxicity of these metabolites. The following list provides examples of the possible products not taken into account by your consideration:

- Dialkyl dithiophosphoric acid moieties as shown in your Appendix 2 of the justification document potentially formed after dissolution of the salts, or Zn-S reduction.
- Dialkyl dithiophosphoric acid moieties may also be formed by exchange of the zinc ion to other metal ions (see the results of hydrolysis studies at pH 9 reported in the IUCLID dossiers). Since zinc is bivalent with four coordination possibilities, but sodium is monovalent such ion exchange leads to two dialkyl dithiophosphate moieties.
- Zinc, zinc oxide or hyroxide formed by above reactions.

- Potential metabolites formed by hydroxylation and further oxidation of the ester alkyl or aryl side chains.
- The alcohol mixtures resulting from spontaneous or enzymatic ester hydrolysis of the neutral and/or basic ZDDP pools metabolically will be converted to a mixture of aldehydes, ketones and carboxylic acids depending on the mixture of initial alcohols.
- Metabolic fate of the basic ZDDP pools and of the individual base oils.
- The parent constituents and their metabolites will form an individual pattern for each ZDDP category member substance in systemic circulation. You do not address the potential interactions due to the co-exposure of biological targets to this chemical mixture.

Conclusion
ECHA concludes that the information presented in your dossier(s) do not support your hypothesis of *"zero or near zero absorption",* and in fact it contradicts it. The expected metabolism pathways lead to different metabolic products, depending on the parent constituents. You did not address the differences in the metabolite products and the consequences for toxicity. You also did not address the potential interactions due to the co-exposure of biological targets to the different metabolic mixtures to be expected for the different constituent pools. Therefore, it is not possible to identify the constituents or their metabolites, which are likely to govern the toxicity profiles of source and target substances. Your claim that the source substance is "*representative for the category as a whole*" is therefore not supported. Consequently, you have not established that substances have similar effects or follow a regular pattern and there is not an adequate basis for predicting the properties of substances within the category from data obtained with a source substance.

*B.2.2. Toxicological profiles*

Annex XI, Section 1.5. provides that *"substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances".* One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

You consider that all category members would have similar toxicity, limited "[..] *to local irritant properties and the complete absence of any evidence of systemic toxicity".*

ECHA notes that based on the information provided in the data matrix (Appendix 4 in the justification document), the category members are generally of low acute toxicity, similar eye irritation and skin sensitisation potential. ECHA notes that for skin irritation the information provided contradicts your claim of similar toxicity: 3 substances are not skin irritants (test material identified as EC: 230-257-6, EC: 224-235-5, EC: 234-277-6), while 9 are classified as skin irritants. You have not explained how the (dis)similar effects can be used to predict the outcome of repeated dose toxicity and developmental toxicity.

You have provided few studies on three ZDDP substances with repeated dose administration (as presented in section B.1 above). In all these studies, the test material is reported solely by name and CAS/EC number. You did not provide information on the ratio of neutral ZDDP pools to basic ZDDP pools, or the concentration and types of base oils present in the actual test materials used to generate the reported experimental studies. Therefore, the results from

the repeated dose toxicity studies do not allow ECHA to establish their relevance to the registered substance(s). However, as these are the only repeated dose administration data that you provided ECHA has analysed it to confirm whether the results support your hypothesis.

Firstly, contrary to your conclusion, ECHA considers that these studies provide evidence of systemic toxicity, in particular:

- In study (i) you reported effects which are regarded as systemic by ECHA: statistically significant changes in organ weights such as decrease in relative kidney to body weight, increase in spleen weight relative to brain weight, increased mean left testes weight relative to brain weight and higher mean right testes weights (absolute and relative to brain) in the highest dose recovery group. These changes cannot be interpreted as secondary to gastrointestinal tract irritation, which was also observed (inflammation, hyperplasya and hyperkeratosis of non-glandular stomach, reported at 160 mg/kg bw/day).

- In studies (ii) and (iii) it is demonstrated that the substance induced mortality, caused clinical signs (hypoactivity, body cool to touch, hunched appearance, unkempt appearance, extremities pale in colour and/or respiratory distress); changes in weights of organs (adrenal, testes, heart, liver) and induced neonatal toxicity. Contrary to your argument that the observed effects "[...] *are considered to be secondary to the primary irritation effects [..]"*, ECHA regards those effects as systemic. More specifically:
  - in (ii) you reported "*gastric submucosal edema*" only for one male in the 250 mg/kg bw and for 4 females in the 500 mg/kg bw and in 3 females in 500 mg/kg bw, "*gastric supportive inflammation*" is reported. You further conclude "*No other test article related histopathological lesions were observed at any dose level*".
  - in (iii) you state "*no microscopic lesions attributed to ZDDP*" are observed. Further, decreased fertility indices (200 mg/kg bw/day) and increased number of dead pups during the post-natal period (100 and 200 mg/kg/day) were also reported. No explanation for these effects was provided.

- Study (iv) has in fact the same deficiencies with respect to the test material description as other studies mentioned above. But you disregarded only this study due to unclear test material composition. ECHA considers that the study results contribute to the toxicity profiles of the substance and need analysis as the other available studies:
  - The study reports statistically significant lower levels of cholinesterase in blood and plasma (all concentrations) and brain (mid and high concentrations), and increased relative brain weight in females (high concentration). ECHA regards these effects as adverse systemic effects.

Also, the presence of systemic effects is demonstrated by other reported toxicological information in the IUCLID dossiers. ECHA notes that following effects, which can be interpreted as systemic, were described: for instances lethargy, piloerection, ptosis, tremors, ataxia, flaccid muscle tone are reported in acute oral toxicity and *in vivo* genotoxicity studies with the test materials identified as EC: 230-257-6; EC: 218-679-9; EC: 272-723-1 or EC: 230-257-6. Also, in sections 7.1. of several IUCLID dossiers you refer to such effects as "systemic" and use them to support your toxicokinetic conclusions (as discussed above in B.2.1)

Furthermore, it appears that the toxicity profiles are not similar.

Secondly, only for zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate), phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts, and zinc bis[O,O-bis(2-ethylhexyl)] bis(dithiophosphate), repeated dose toxicity studies are reported. There is no explanation provided why these three substances are sufficient to cover the structural diversity of the ZDDP category member substances. There is no other bridging information available for repeated dose toxicity for any of the other substances, their constituent pools or their metabolites – acute toxicity data is not sufficient to establish the toxicological profile of a substance with regard to repeated dose toxicity and reproductive toxicity.

Thirdly, you claim that the basic ZDDP pools do not significantly impact the toxicological properties of the substances. However, your assumption is not substantiated by any scientifc justification or experimental results.

Fourthly, with regard to the base oils in the registered compositions, you state that they are "*chemically inert*" and that their content and identity "*is considered not to influence the potential for systemic toxicity, as described in the category document and primarily because toxicokinetic studies have shown the mineral oil not to be absorbed at toxicologically significant levels*". ECHA notes that you did not report any composition of the base oils nor provided any experimental data with them to substantiate your claim. Further, the base oils with the EINECS numbers provided are classified as Carc Cat 1B. You claim that they are highly refined and meet "Note L" of the CLP Regulation[6], but there is no proof provided.

Conclusion for toxicity profiles

ECHA considers that you have not provided any information that would support your claim that the substances of the ZDDP category do not cause systemic toxicity. In fact, the available information contradicts your claim. Therefore, this information is not sufficient to predict that substances in the ZDDP category have similar adverse properties or are likely to follow a regular pattern.

*B.2.3. Supporting information proposed*

As explained above under B.2.1 and B.2.2, the data do not support your hypothesis of no absorption and no systemic toxicity. You seem to have recognised the lack of supporting information as you intend to test the source substance in an 'enhanced' 21-day range-finding study "*to determine if the prediction of very low absorbance and no systemic exposure are valid*". Generally, it is at your discretion to generate and provide any supporting information that you consider may justify your hypothesis. However, ECHA notes that it is unclear whether this objective could be fulfilled by the outcome of such a test. In particular the following is noted:

Firstly, the validity of the proposed test seems questionable as you have not indicated that you intend to follow any OECD guideline nor GLP.

Secondly, the relevance of the study protocol to the pursued objective of determining "*if the prediction of very low absorbance and no systemic exposure are valid*" seems questionable. In particular, it is unclear what compositions would be tested, how many animals per

[6] Note L: The classification as a carcinogen need not apply if it can be shown that the substance contains less than 3 % DMSO extract as measured by IP 346 "Determination of polycyclic aromatics in unused lubricating base oils and asphaltene free petroleum fractions - Dimethyl sulphoxide extraction refractive index method", Institute of Petroleum, London. This note applies only to certain complex oil-derived substances in Part 3.

sex/per dose group would be in the study, how the doses would be selected, which haematological and biochemical parameters would be measured, for which organs histopathological examinations are foreseen. Further it is not clear which target constituents or break down products would be subject to analytical determinations for toxicokinetic parameters.

Thirdly, you did not demonstrate the relevance of the proposed study performed on the source substance (or on two extra source substances considered for potential future testing) for other substances in the ZDDP category, including the substance subject to the present decision. As you have not demonstrated that the source substance is representative for other substances in the ZDDP category, the results of the proposed study will provide information only for the substance tested and not for other substances in the category.

### C. Conclusion on the grouping and read-across approach

Based on the above considerations ECHA concludes that you have not provided adequate and reliable information to demonstrate that the proposed read-across approach is plausible for the endpoints in consideration. ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are not met, and consequently the testing proposed on the source substance is not appropriate to fulfil the information requirement of the substance subject to the present decision.

### 1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substance phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (EC no 270-608-0).

In addition, in your updated dossier (submission number [redacted] you have provided some arguments why you consider that testing for this standard information requirement is not needed. You have stated that the registered substance has "*very low absorption potential*" and that "*The alkaryl ZDDPs are not expected to cause target organ/repeated dose or developmental toxicity*".

ECHA has assessed the information provided and have observed the following:

To adapt standard information requirement for 90-day repeated dose toxicity, the conditions of specific adaptation based on Annex IX, Section 8.6.2, Column 2, or General adaptations, set in Annex XI have to be fulfilled.

You have not specified which of the above adaptation options you intended to use. The arguments you provided in your dossier (as cited above) do not fulfil the conditions set neither in Annex IX, Section 8.6.2, Column 2 nor in Annex XI. Hence, your adaptation is rejected, the standard information requirement is not fulfilled and further testing is necessary.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance. As explained in section "Grouping of substances and read-across approach" above, your adaptation of the information requirement is not accepted. Hence, there is a need to test the registered substance.

ECHA considers that a sub-chronic toxicity study (90-day) with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation. ECHA notes that the registered substance contains [redacted] in the neutral and basic constituent pools. This phenol moiety in the degradation product [redacted] (see Appendix 2 in the justification document) fits well the notion of what might be an endocrine-active chemical by the possibility to bind to the estrogen receptor. The recently updated OECD TG 408 investigates endocrine sensitive endpoints intended to improve detection of potential endocrine activity of test chemicals.
Therefore, due to the suspected ED potential of the registered substance, the test shall be conducted as described in the guideline version adopted on 27 June 2018.

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

You proposed testing by the oral route. 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 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration for the registered substance. More specifically, the substance is a liquid of very low vapour pressure. Uses with industrial (PROC 7) and professional (PROC 11) spray application are reported in the chemical safety report. However, the reported concentrations are low [redacted] Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study with the registered substance: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408), while your originally proposed test for Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) with the analogue substance (phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (EC no 270-608-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

The testing material used for performing the required study shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

*Notes for your considerations:*

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (Annex X, 8.7.3.). However, this testing proposal is not addressed in this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the Extended one-generation reproductive toxicity study. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your testing proposal for the Extended one-generation reproductive toxicity study. The updated testing proposal should include a justification for the design of the Extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the Sub-chronic toxicity study (90-day).

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 with the analogue substance phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (EC no 270-608-0).

In addition, in your updated dossier (submission number [redacted]) you have provided some arguments why you consider that testing for this standard information requirement is not needed. You have stated that the registered substance has "*very low absorption potential" and* that "*The alkaryl ZDDPs are not expected to cause target organ/repeated dose or developmental toxicity*". You have also indicated that the registered substance is already classified as Repro 1B, based on the presence of an impurity (Phenol, dodecyl-, branched; CAS 121158-58-5). You considered that, "*according to stage 1.1 of section R.7.6.2.3.2 of Chapter R.7a, additional reproductive toxicity testing for any annex is not required*".

Even though, you did not explicitly claim such adaptations, we understand that you consider the adaptations possibility according to Annex IX, Section 8.7., Column 2, third indent and the second paragraph.

ECHA has assessed the information provided and have observed the following:

A. According to Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, namely:

- That there is no evidence of toxicity seen in any of the tests available; and
- That it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- That there is no or no significant human exposure.

None of the conditions are met. In particular:

- You have not demonstrated that the registered substance do not cause toxicity in relevant tests. There are no repeated-dose, reproductive and/or developmental studies performed with the registered substance which could provide relevant evidence.
- You have not provided any toxicokinetic data to show that there is no systemic absorption.
- The uses of the Substance indicate that there is significant human exposure

B. According to Annex IX, Section 8.7., Column 2, second paragraph, the study does not need to be conducted if the substance meets the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment. However, testing for developmental toxicity must be considered.

You have self-classified the Substance as Repro 1B for fertility, based on the impurity (Phenol, dodecyl-, branched; CAS 121158-58-5). However, you have not justified why the Repro 1B self-classification for sexual function and fertility is sufficient to protect pregnant females and their foetuses, and why information on developmental toxicity is not needed for your Substance.

Hence, your adaptations are rejected, the standard information requirement is not fulfilled and further testing is necessary.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance. As explained in section "Grouping of substances and read-across approach" above, your adaptation of the information requirement is not accepted. Hence, there is a need to test the registered substance.

ECHA considers that the pre-natal developmental toxicity study with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation. ECHA notes that the registered substance contains [redacted] phenols in the neutral and basic constituent pools. This phenol moiety in the degradation [redacted] (see Appendix 2 of your justification document) fits well the notion of what might be an endocrine-active chemical by the possibility to bind to the estrogen receptor. The recently updated OECD TG 414 investigates endocrine sensitive endpoints intended to improve detection of potential endocrine activity of test materials.

Therefore, due to the ED potential of the registered substance, the test shall be conducted as described in the guideline version adopted on 27 June 2018.

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

You proposed testing by the oral route. ECHA agrees 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 liquid, ECHA concludes that testing with the registered substance should be performed by the oral route.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the study with the registered substance: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414), while your originally proposed test for Pre-natal developmental toxicity study in a first species (test method: OECD TG 414) with the analogue substance (phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (EC no 270-608-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

The testing material used for performing the required study shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

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

**Deadline**

In the draft decision communicated to you, the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision you requested up to 45 months for the conduct of the requested tests (OECD TG 408, OECD TG 414 in rat), and provided supporting information from two CROs.

The information provided indicates timelines for conducting 3 studies: the two above mentioned studies and in addition an OECD TG 414 test in rabbits, in a step-wise manner. It considers 36-40 months as sufficient, including the "*study completion, reporting, risk assessment and dossier completion*".

Taking into account that you are not requested to provide 3 but 2 studies a reasonable time period for providing the required information in the form of an updated registration is 24 months from the date of the adoption of the decision. However, taking into account the possible lab capacity issues, ECHA gives you 6 more months. Therefore, the deadline for the submission of the results from the OECD TG 408 and OECD TG 414 in one species is extended from 24 to 30 months. The decision was therefore modified accordingly.

## Appendix 2: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 25 June 2018 following the necessary clarification of the substance identity issues related to several members of the ZDDP category.

ECHA held a third party consultation for the testing proposals from 4 October 2018 until 19 November 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **6 March 2019**, 30 calendar days after the end of the commenting period.

The registrants updated the registration with submission number [redacted] on 06 March 2019. ECHA took the information in the updated registration and in the registrants' comments into account and modified the draft decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

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

**Appendix 3: Specifications regarding the testing material**

**Issues related to the composition of the registered substance and its consequence on the test material for requested studies**

You reported within the joint submission the registered substance as Zinc bis[bis(tetrapropylenephenyl)] bis(hydrogen dithiophosphate) (EC no: 234-277-6). The substance is registered as Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB Substance). It is a zinc dithiodialkylphosphate (ZDDP) consisting of neutral and basic zinc salts as constituents, which are also UVCB. In addition, base oils are reported as constituents. The base oils are refined crude oils and UVCB substances.

The main constituents and their concentration ranges in the boundary composition are:

[redacted]

ECHA notes that the substance is classified as Repro 1 B (H360F) due the presence of tetrapropylene phenol (=TPP, or Phenol, dodecyl-, branched Phenol, alkyl branched (species comprising decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl substituents), EC no 310-154-3) in the composition. This constituent is not listed in the boundary composition. In the legal entity composition this constituent has a concentration value of [redacted] with a typical concentration of [redacted]

Due to the wide ranges of reported constituent concentrations for the joint submission, possible compositions may be e.g.

[redacted]

- any composition between these concentration values.

It is not clear whether [redacted] is also a realistic possibility. In addition, different base oils with non specified compositions may be present at various concentrations. You state in your testing strategy for the ZDDP category that the ratio of the constituents does not influence the potential for systemic toxicity, since the constituents are not absorbed at a significant level. However, you did not provide any experimental proof for this assumption and in fact it is contradicted by the information (see Appensix 1, section B.2).

ECHA therefore considers it likely that the different possible constituent ratios result in different hazard properties, if tested in toxicity studies. To avoid underestimation of the hazard caused by the inappropriate selection of the test material, the test material should represent a worst case in terms of expected absorption and expected toxicity. ECHA

therefore provides considerations on the selection of the test material and how it should be reported below.

**1- Selection of the test material(s)**

It is the responsibility of all registrants of the substance to agree on the composition of the test material in carrying out the tests required by the present decision. It is important to select the test material so that it is relevant for all the registrants of the substance, i.e. it takes into account the variation in compositions reported by all members. The composition of the test material(s) must fall within the boundary composition(s) of the substance, taking into account as well the TPP content (as indicated in Appendix 1 and below).

Studies conducted to investigate the hazardous properties need to use test material representative for the registered substance.

While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the registered substance is known to have an impact on (eco)toxicity, the selected test material shall contain that constituent/impurity. For the registered substance, this consideration applies to the constituent [redacted]

As explained above, the registrants of the joint submission for this substance should select a composition of the test material for the conduct of the requested studies, which represents a worst case in terms of expected absorption and expected toxicity for the possible constituent ratios. In this regard the specification of the ratio between the concentrations of the [redacted] and the concentration of the [redacted] and the concentration of the base oils appears to be a relevant consideration. You also state that the [redacted] exist in reversible monomeric and dimeric forms. It is not clear which conditions lead to which form in this equilibrium. Therefore, the extent of dimer formation from the [redacted] appears to be also a relevant consideration for the selection of the appropriate test material. You also provide the structure of a [redacted] which may be formed from the [redacted]. The possible formation of such hydrolysis/ degradation product during the test material administration appears to be also a relevant consideration for the selection of the appropriate test material.

The following aspects therefore may facilitate the selection of the appropriate test material. ECHA considers that in the absence of toxicity data for the individual constituents, one parameter currently available to support the selection of the test material in a worst-case approach is the molecular weight. The [redacted] consists of [redacted] whereas the [redacted] consists of [redacted]. In addition, due to the difference in molecular weight between the monomer and the dimer, it is important to know what percentage of the [redacted] exists as dimer in the test material. In general, the [redacted] is more likely to be absorbed than the [redacted]. Moreover, the

[redacted] may be more easily hydrolysed/degraded to the [redacted] in the stomach thereby further increasing the likelihood of absorption. Furthermore, the base oil possibly present in the composition have an unknown impact on the absorption of the ZDDP constituents. Lower concentrations of the base oil likely will have a smaller impact and their presence in the test material should be as low as technically possible. The constituent [redacted] should be present in its typical concentration of [redacted]

**2- Technical reporting of the test material**

The composition of the selected test material must be reported in the respective endpoint study record, under the test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the registered substance and to all the registrants of the registered substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website (https://echa.europa.eu/documents/10162/22308542/manual_regis_and_ppord_en.pdf).

In that respect, ECHA notes that the substance is registered as Substance of Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB Substance). By definition, the composition of such substances is complex, the number of constituents is relatively large, the composition is, to a significant part, unknown, and/or the variability of the composition is relatively large. All of the constituents identified in the composition reported in the dossier have a broad variation.

According to Article 13(4) of REACH, tests and analyses required under this Regulation shall be carried out in compliance with the principles of Good Laboratory Practice (GLP). The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test item and description of its characteristics.

More specifically, according to Article 13(3) of REACH, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

To conclude, for the test material selected to conduct the requested studies, information as specified below has to be provided:

Detailed information on the composition of the test material using appropriate analytical techniques. The reporting must include the concentration values of the [redacted] the concentration values of the [redacted] the concentration values of the [redacted]

[redacted] the concentration values of [redacted] and the concentrations, identities and composition of the base oil.

You have to justify the test material selected for testing taking into account the aspects on absorption described under 1 above.