EUROPEAN CHEMICALS AGENCY

Helsinki, 27 September 2019

Addressee: [redacted]

Decision number: TPE-D-2114484202-55-01/F
Substance name: Zinc bis[O-(6-methylheptyl)] bis[O-(sec-butyl)] bis(dithiophosphate)
EC number: 298-577-9
CAS number: 93819-94-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05/03/2019
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

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

While your originally proposed tests for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) and Pre-natal developmental toxicity study (OECD TG 414) using the analogue substances: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6); Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8); Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5); Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1) are 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 study 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 X, 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).

This decision does not any longer address your testing proposal to fulfil the information requirement for a developmental toxicity study in a second species. The results of the pre-natal developmental toxicity study in a first species, among other relevant information, may inform on the choice of a test substance appropriate to fulfil information requirement for a developmental toxicity study in a second species for the registered substance.
Therefore, your testing proposal for a developmental toxicity study in a second species will be addressed separately, after having received the results of the pre-natal developmental toxicity study in a first species.

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[O-(6-methylheptyl)] bis[O-(sec-butyl)] bis(dithiophosphate) (CAS No: 93819-94-4, EC No: 298-577-9, 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.)

You propose to test the analogue substances and 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 proposed for the "ZDDP category".

ECHA notes that in your updated dossier (submission number [redacted] you have modified your testing strategy and proposed new analogue substances to be tested.

In the original dossier you have proposed 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), while in the updated dossier you are proposing to test 4 substances, as follow:

1. Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6)
2. Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8)
3. Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5)
4. Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1)

ECHA has addressed your testing strategy of using these new analogue substances, hereafter referred as source substances.

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 updated registration dossier you have provided the following documents as separate attachments in IUCLID Section 13:

[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 "justification document"). The document contains an updated 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] Hereafter, ECHA refers to the two testing proposal documents as "testing strategy". Both documents present your new "intelligent testing strategy" and give 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] *to* [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]

In the updated dossier you proposed a category of 13 substances, all alkyl ZDDPs. The substances are further divided into 4 sub-categories, based on the following parameters:

- Molecular Weight (MW)
- Type of starting alcohol (linear, primaryl linear, branched; branched, secondary; mixed)
- Amount of diluent oil
- Concentration of basic vs neutral ZDDP pools

Summary of the new grouping is presented in the table below.

Type	EC number	CAS number	EC Name
Linear, primary	230-257-6	6990-43-8	Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate)
Branched, primary	270-478-5	68457-79-4	Phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts
	247-810-2	26566-95-0	Zinc bis[O-(2-ethylhexyl)] bis[O-(isobutyl)] bis(dithiophosphate)
	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)
Branched, secondary	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
	218-679-9	2215-35-2	Zinc O,O,O',O'-tetrakis(1,3-dimethylbutyl) bis(phosphorodithioate)
Mixed	270-608-0	68457-79-4	Phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) 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
	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

Table 1. Substances specified as members of the ZDDP category

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.

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

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.

A.2.1. Compositional similarities and differences

In your category justification document you reported concentration ranges for the average contents in neutral ZDDP, basic ZDDP and base oils in the composition of the members of the category. You did not provide information on the variability in the concentrations of each of these pools of constituents for each category member. Details on the minimum and maximum concentrations for each pool of constituent for the different members of the category is necessary to characterise the variability in the composition of the individual category members. This information is required for a meaningful comparison of the compositions of the category members in order to confirm their compositional similarities. Based on the information provided in the technical dossiers of the individual category members, the concentrations of the different pools of constituents can vary broadly. These variations are not represented and accounted for when focusing on the average concentrations of each pool of constituent.

Furthermore, according to the information provided in the category justification document, "*the substances contain various base oils*" and "*there may be 1 to 6 base oils added to the ZDDPs*". You have identified 10 different base oils which are included in the composition of the category members. You also reported a numerical value for the overall percentage of base oil in the composition of the category members . However you have not provided any information on the identity of the base oils present in the composition of the category members. This information is required for a meaningful comparison of the compositions of the category members in order to confirm their compositional similarities

A.2.2. Applicability domain

In your category justification document you describe the applicability domain based on the molecular weight and alkyl chain length of the constituents of the substances, the nature of the starting alcohol (linear, primaryl linear, branched; branched, secondary; mixed), the amount of diluent oil and the concentration of basic vs neutral ZDDP pools. On that basis, you identified the substances included in the ZDDP category.
No inclusion/exclusion criteria are presented. In particular, you did not provide criteria based on structural elements for the inclusion/exclusion of esters formed from primary, secondary or tertiary alcohols of defined carbon chain length and characterised branching. You did not provide criteria for the allowed quantitiative variations in the concentrations of pools of constituents in the compositions of the group members. ECHA considers that under these circumstances the boundaries of the applicability domain are not defined and that the borders of the category are not clearly established.

A.3 Conclusion on strucural similarities and the grouping.

ECHA concludes that the information provided on the category members does not reflect the inherent variability in the concentrations of the constituents and does not constitute a reliable basis to establish compositional similarities. The applicability domain does not indicate clearly the borders of the category and does not unambiguously establish for which chemicals the category does not hold.

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 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 use the following assumptions to support the prediction of properties of the registered substance from data for the source substances:

- ZDDPs are "*predicted to have low absorbance via the oral route and consequently systemic exposure will also be low*";
- In addition, you claim that upon ingestion the only relevant pool of constituents is the neutral pool;
- *"The alkyl dithiophoaphte ester (DTPE, dissociated from Zn) is the only form in the GI fluid and is therefore the only bioavailable portion"* and is regarded by you as *"reactive chemistry of interest";*
- *"ZDDPs are all metabolized similarly to the starting alkyl alcohols";*
- *"the nature of the alkyl substituent groups (primary, secondary, mixed), and the ratio of neutral to basic ZDDP, have no significant impact on the toxicological properties of the substance*";
- *"the presence of mineral base oil, at various levels, has no interaction with the ZDDP complex*". You further postulate that the "*amount of the diluted oil is only expected to influence the bioavailability*".

You provided the following considerations regarding toxicokinetic properties and the results of toxicity tests.

B.1.1. Toxicokinetic properties

- *Hydrolysis and absorption*

You consider that the molecular weight of the constituents exceeds the cut off value of 500 and therefore does not favour passive absorption of these constituents unchanged. You further indicate that the water solubility/lipophilicity of these consituents also negatively influence their absorption. In addition, "low" absorption is predicted using SwissADME.

In the updated dossier you claim that the basic form of ZDDPs is "*quickly and completely broken down into the neutral form",* therefore "*the only relevant pool is the neutral pool*". You indicate that the neutral ZDDPs are hydrolysed to form alkyldithiophosphate esters (DTPEs) which you identify as "*the only form in the GI fluid and is therefore the only bioavailable portion"* and as the "*reactive chemistry of interest*". You assume that the percentage of base oil in the composition of the category members will impact the absorption of the constituents so that "*ZDDPs with more base oil will have less bioavailability*".

In order to establish the rapid and complete conversion of basic ZDDPs to neutral ZDDPs and then into DTPE and Zn you have provided the following information:

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

1. Simulated gastric fluid study (preliminary data) in which you tested *"[...] ZDDPs made from both primary (relatively high initial basic ZDDP) and secondary (relatively low initial basic ZDDP) alcohols".* You concluded that *"The basic form was converted to neutral within 5 minutes (secondary) or 15 minutes (primary – likely slower than primary due to higher starting amounts of basic) [...]".*
2. Studies using NMR analysis [redacted] 2010) in which you tested the category member EC 283-392-8 (secondary, branched). Results from these investigations reveal that at pH 4 the Zn salt is dissolved, and that the DTPE no change (the P species transformed after 5 days at 50°C). At pH 9, only DDP is detected in the aqueous phase, no Zn is detected. White insoluble mass (ZnO or Zn phosphate) is formed.

Metabolism

You state that the ZDDPs undergo *"common biotransformation pathway to molecules that also have a consistent and predictable toxicological outcome"* (dithiophosphate esters (DTPEs) and alkyl alcohols).

To support your statement, you reported data from metabolic modelling, using OASIS TIMES v.2.28.1.4 *in vivo* rat simulator, v.07.11, for 3 ZDDP members: 1) Mixed primary alcohol EC 270-608-0; 2) Linear primary alcohol EC 230-257-6; 3) branched secondary alcohol EC 283-392-8. You concluded: *"Metabolism modelling demonstrates a common metabolic pathway resulting in transformation to the starting alcohol, rendering these a predictable variable in the category in terms of ZDDP toxicity".*

B.1.2. Results of toxicity studies

You interpret the results obtained in acute and repeated dose toxicity studies as indication of lack of systemic effects.

You provided information on repeated dose toxicity as follows:

(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". 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"*).

In the updated justification document you provided some considerations (but no studies), regarding the toxicity of the biotransformation products DTPEs and the toxicity of CAS: 53378-51-1 (sodium O,O-diisobutyl dithiophosphate).

You also presented summary tables with information on the harmonized classification of the alkyl alcohols and the base oils in order to establish the absence of toxicity of these constituents/biotransformation products.

Further, you provided results from *in vitro* mechanistic studies, performed for 10 ZDDPs and 4 base oils in order to demonstrate *"similar biological activity"* of the ZDDP members.

B.1.3. Selection of the source substances to be tested

In your updated testing strategy you have identified 4 ZDDP substances to be tested. You justify the selection of the source substances as being *"representative of the sub-categories, and will adequately cover the entire category for subsequent Annex IX and X testing".* Further, you have summarized how you intend to use the generated experimental data to read-across for the other members of the categoty (Table 4 in the testing startegy).

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

ECHA understands that your hypothesis is that the substances in ZDDP category have:

- structural similarity (core common functionality)
- similar toxicokinetic properties
  - low absorption, the dithiophosphate ester group the only absorabbale moity;
  - similar metabolic pathways
  - common metabolic products
- similar toxicological properties, more specific lack of systemic toxicty.

Based on the above hypothesis you propose to predict the relevant toxicological properties of the substances in ZDDP category by the results obtained on the selected category members, in a read-across approach.

In the following, ECHA examines whether your hypothesis holds in order to determine whether testing the source substances allows prediction of the relevant properties, and therefore fulfilment of the information requirements, of the substances in the ZDDP category, including the substance subject to the present decision.

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.

Hydrolysis and absorption

ECHA has the following observations with regard to your claims regarding conversion of basic ZDDPs to neutral ZDDPs and then into DTPE and Zn:

In your updated dossier you claim that "*the varying concentrations of basic ZDDP among category members is not relevant*" due to its quick and full hydrolysis to the neutral pool. Further, you state that the neutral ZDDP will dissociate in the gastrointestinal tract (GIT) and will be further transformed to the DTPE. To demonstrate theses you provided two studies (1 and 2 described above, under B.1.). However, these studies do not support your claims, for the following reasons:

Regarding the information from study 1:
The results from this study show different hydrolysis rate for the study conducted with claimed relatively low and high concentration of basic ZDDP. So, contrary to your claim the studies show that the differences in the basic ZDDP concentration do affect the speed of hydrolysis. However, as the composition of the test material and in particular the initial concentration of the basic ZDDP pool is not provided, it is not possible to dismiss the difference observed. In particular, bearing in mind that variations in the basic ZDDP pool concentrations vary considerably (from [redacted]

Regarding the information from study 2:
ECHA understands that this study looks at the dissociation of the ZDDPs in aqueous conditions. Firstly, there is no information on the composition of the test material and from the study description it is not clear what has been tested. Secondly, the study conditions (temperature 50°C and pH higher than the stomach) do not resemble those in the gastro-intestinal tract. Therefore, the results are irrelevant to support your claim of transformation of neutral ZDDP to DTPE in the GIT. Additionally, regarding the different type of alcohols, you did not explain if the different type of alcohols would affect the hydrolysis rate and whether this would impact the prediction.

Therefore, you have not provided evidence to substantiate your claim that *the "varying concentrations of basic ZDDP among category members is not relevant".*

Metabolism

ECHA has assessed the data reported from the metabolic modelling (OASIS TIMES v.2.28.1.4 *in vivo* rat simulator, v.07.11) and have identified the following deficiencies of the hypothesis you are making and data you present to support it:

Firstly, bearing in mind the structural differences of the parent compounds, formation of different intermediate metabolites is anticipated. Although you acknowledged that it is of great importance to "[...] *understand the toxicity of each biotransformation stage*" you did not identify the intermediate metabolites formed and did not provide qualitative and quantitative information on the formation of these intermediate metabolites.

Secondly, you did not elaborate on the impact of the exposure to the intermediate metabolites on the toxicity of the substances. You further postulated that the alkyl dithiophosphate ester moiety (DTPE), formed as a result of biotransformation of the neutral ZDDP pool, is the "*reactive chemistry of interest*". However, you have not demonstrated that indeed the DTPE will be the only biologically active moiety.

Therefore, it is not possible to verify your assumption that the toxicological properties of the category members depend mainly on the end metabolites: dithiophosphate esters and alkyl alcohols.

As a conclusion ECHA considers that you have not provided sufficient information on the absorption and metabolism of the ZDDP members which would allow to assess the qualitative and quantitative internal systemic exposure of the test organism and confirm your hypothesis.

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: 2 substances are not skin irritants (test material identified as EC: 230-257-6, EC: 224-235-5), 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 somestudies on three ZDDP substances with repeated dose administration (as summarized 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 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 interpeted 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).

In your updated read-across justification document you did not provide any new experimental data with the category members to support your statement of lack of systemic toxicity.

Instead, you provided some considerations (but no data) regarding the toxicity of the biotransformation products (DTPEs and the alkyl alcohols), as well as for the base oils, seemingly to support your statement of "lack of toxicity".
However, these considerations do not support your claim, for the following reasons:

- Toxicity of DTPEs

For DTPEs you did not provide any data relevant to the toxicological properties under consideration, such as repeated-dose toxicity or reproductive/developmental toxicity studies.

Instead, you refer to a REACH registration with CAS: 53378-51-1 (sodium O,O-diisobutyl dithiophosphate) that contains OECD TG 422 and OECD TG 414 studies. ECHA notes that the substance is not part of the ZDDP category. You did not provide any explanation why you refer to this substance in your justification, what is its relation to the DTPEs and why you would consider this information relevant to predict the toxicological properties of the ZDDP members.

- Toxicity of alcohols

For the alkyl alcohols, you provided a summary table on GHS (Table 4 in the updated Justification document) and concluded that "*none of the alcohols are classified for reproductive toxicity based on conclusive information. [...] the alcohols have a common health hazard as irritants".* However, this is irrelevant, as lack of harmonized classification does not mean that no toxicity is observed.
Further, you have not addressed the possibility of synergistic effects when there is concurrent exposure to alcohols and other ZDDP components and how this may impact the prediciton.

- Toxicity of base oils

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 the composition of the base oils nor have you provided any experimental toxicokinetic or toxicity data with them to substantiate your claim. Instead you provided a summary table on GHS (Table 2 in the updated Justification document) and concluded that "*None are classified as hazardous to human health based on conclusive studies, and their presence in potential ZDDP test items would not be expected to contribute directly to the hazard profile".* However, this is irrelevant as the lack of harmonized classification does not mean that no toxicity is observed. Further, you have not addressed the possibility of synergistic effects when there is concurrent exposure to base oils and other ZDDP components and how this may impact the prediciton.

- *In vitro* mechanistic investigations

Further, in the updated justification document you have presented results from Toxys ToxTracker *in vitro* mechanistic study in order to demonstrate "*similar biological activity*" of the ZDDP members.

The study was performed with 10 ZDDPs and 4 base oils. None of the 4 base oils showed cytotoxicity. All ZDDPs exhibited cytotoxicity. Three of the four base oils did not activate any of reporter genes at all concentrations tested. Nine out of ten ZDDPs induced oxidative stress pathways and activated the unfolded protein response. Based on these results you concluded that the ZDDPs "*have very similar modes of action (oxidative stress and unfolded protein response) when causing cellular toxicity*".

ECHA aknowledges that similar results have been obtained from the individual mechanistic assays conducted on the different substances, suggesting similar properties for the endpoints tested. However you did not explain how the reported results would support your hypothesis for lack of systemic toxicity. Further, ECHA points out the complexity of the systemic interactions and the reproductive process and the large number of targets/mechanisms associated with those broad areas of toxicity. You did not discuss how the results from these mechanistic studies would be used to predict for complex endpoints such as repeated dose toxicity and developmental toxicity.

Conclusion for toxicity profiles

ECHA considers that you have still 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. Source substances – prediction

You identified 4 substances as "*representatives of the sub-categories*" and proposed to test them in 90-day repeated dose oral toxicity studies and pre-natal development toxicity studies to fulfil the standard information requirements of Annex IX, Section 8.6.2. and 8.7.2 applying to the category members.
From Table 4 in your testing strategy document it appears that you intend to use the data generated for the individual representative substances to predict the toxicological properties for the other members of their sub-categories. As an example you state that the data to be generated with the source EC: 224-235-5 (branched, primary) will be used to predict the properties for the members in the same sub-category.

However, ECHA notes that in the IUCLID dossiers of all category members, with the exception of one (EC No 230-257-6) you have submitted testing proposals proposed to be conducted with these 4 substances. This suggests that you intend to use the data obtained from these 4 source substances to predict the properties for all category members.

Based on the above, ECHA considers that you did not explain in a clear and unambiguous way how exactly the data proposed to be generated will be used to predict the toxicological properties of the substances in the ZDDP category, including the substance subject to the current decision.

B.2.4. Supporting information proposed by you to be generated in the future

You have recognized the lack of supporting information and you intend to generate more data in order to substantiate your read-across hypothesis. In particular, you have expressed the following considerations and intentions:

1. You consider investigating the absorption potential and metabolism of 13 ZDDPs in *in vitro* toxicokinetic studies;
2. You intend to explore the biological reactivity of the ZDDPs to support the similarity in their mechanism of action.
3. You intend to carry out *in vivo* toxicokinetic studies (OECD TG 417) for the 4 source substances, in order to, among others, verify your hypothesis for low absorption and clarify the influence of the base oils.

ECHA recognises your intention to generate experimental data to support your read-across hypothesis. Data on toxicokinetic properties and mechanism of action of the category members may contribute to establish similarities in these properties between the members of the category. However, ECHA is not in a position to conclude on the relevance and/or adequacy of the data obtained from these investigations for the purpose of supporting your predictions for the reasons provided below, and generation of these data is at your own discretion:

Firstly, although toxicokinetic data is in general valuable supporting information for a read-across hypothesis, the inherent complexicity of the composition of UVCBs complicates its interpretation. You did not explain how you intend to address this complexity in the course of the proposed *in vitro* and/or *in vivo* experiments, in order to obtain definitive conclusions on the absorption and metabolism properties of the different constituents of the ZDDPs.

Secondly, you have not provided any details on the design of the tests that you consider to conduct. Similarly, you have not provided any criteria for the assessment of the results of these tests, including what would be considered as "low absorption". This is of utmost importance as your read-across hypothesis is based on an anticipated low absorption of the substances and the results from these studies may or may not confirm this hypothesis.

Thirdly, with regard to the mechanistic studies that you intend to generate, it is unclear what is their relevance to your hypothesis, as already noted in section B.2.2. above, other than establishing similarities in biological activity of the category members for the cellular signalling pathways tested in these assays.

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 substances is not appropriate to fulfil the information requirements 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 testing proposals for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substances: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6); Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8); Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5);

Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1).

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 the 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.

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 agrees 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 and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

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 tests for Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) with the analogue substances: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6); Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8); Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5); Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1) are 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 testing proposals for a pre-natal developmental toxicity study in rats according to OECD TG 414 with the analogue substances: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6); Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8); Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5); Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1).

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.

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 subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414), while your originally proposed tests for Pre-natal developmental toxicity study in a first species (test method: OECD TG 414) with the source substances: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate (CAS:6990-43-8; EC: 230-257-6); Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-Pr) esters, zinc salts (CAS:84605-29-8; EC: 283-392-8); Zinc bis(O,O-diisooctyl) bis(dithiophosphate) (CAS: 4259-15-8; EC: 224-235-5); Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-Pr) esters, zinc salts (CAS: 68909-93-3; EC: 272-723-1) are 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:

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.

ECHA also notes that your testing proposal for a developmental toxicity study in a second species is no longer addressed in the current decision and will be addressed separately, after having received the results of the pre-natal developmental toxicity study in a first species.
The results of the pre-natal developmental toxicity study in a first species, among other relevant information may inform on the choice of a test substance appropriate to fulfil information requirements for a developmental toxicity study in a second species for the registered substance.

Deadline

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

The information provided indicates timelines for conducting the three above mentioned studies, in a step-wise manner. It considers 36-40 months as sufficient, including the "*study completion, reporting, risk assessment and dossier completion*".

As the testing proposal for the PNDT (OECD TG 414) in the second species is no longer addressed in the present decision, we consider that a reasonable time period for providing the currently 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 5 March 2019. ECHA took the information in the updated registration and in your 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[O-(6-methylheptyl)] bis[O-(sec-butyl)] bis(dithiophosphate) (EC no: 298-577-9). 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]

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 Appendix 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. 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.

As explained above 1, 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] structures. 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 dimer or than [redacted]. Moreover, the [redacted] may be more easily hydrolysed/degraded to [redacted] in the stomach thereby further increasing the likelihood of absorption. Furthermore, the different base oils possibly present in the composition have an unknown impact on the absorption of the ZDDP constituents. Lower concentrations of base oils likely will have a smaller impact and their presence in the test material should be as low as technically possible.

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] and the concentrations, identities and compositions of the base oils.

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