~~Confidential~~

Helsinki,17 April 2023

Addressees
Registrant(s) of JS_218-679-9 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
06/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Zinc O,O,O',O'-tetrakis(1,3-dimethylbutyl) bis(phosphorodithioate)
EC number: 218-679-9

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information under request 1 below by ***23 July 2026***; and all other requested information listed below by ***23 July 2027***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats;

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat);

Information required from all the Registrants subject to Annex X of REACH

3. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit).

Your testing proposals for the above mentioned tests 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) or unspecified substances from ZDDP category are rejected.

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed

in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

Contents

0. Reasons common to several requests

1 The decision of ECHA is based on the examination of the testing proposals submitted by you, in your dossier for the Substance: Zinc O,O,O',O'-tetrakis(1,3-dimethylbutyl) bis(phosphorodithioate) (EC number: 218-679-9).

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

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

3 In IUCLID, Sections 7.5.1 and 7.8.2, you propose to test analogue substances and use the results obtained to adapt the above indicated 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".

4 You are proposing to test 4 analogue substances, as follows:

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)

5 In addition, you are proposing to test unspecified substances from ZDDP category for information requirement of Annex X, Section 8.7.2.

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

7 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.

8 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*".

9 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.

10 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

1.2. Assessment of the read-across approach

11 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, 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.

12 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Scope of the grouping of substances (category)

13 In your registration dossier you propose a category of "ZDDP". The category consists of 13 substances, all alkyl ZDDPs. You provide the following documents as separate attachments in IUCLID Section 13:

- "[redacted]

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

15 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".*

16 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."*

17 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."*

18 This is further explained "*ZDDP substances are manufactured and distributed in commerce in highly refined lubricant base oil ([redacted]). The oil is added during the neutralization of the dithiophosphate alkyl esters intermediate with zinc oxide. The oil acts as a solvent and stabilizer in the reaction, manages the viscosity and improves consistency of the final product. The majority of the ZDDP substances are never isolated from base oil at any time during their life cycle.*"

19 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] or [redacted]%.* "

20 The category members 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.

21 Summary of the 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

22 Table 1. Substances specified as members of the ZDDP category

23 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 category members.

24 We have identified the following issues with the proposed scope of the grouping:

0.1.1.1. Compositional similarity and differences

25 Under Annex XI Section 1.5, Structural similarity for UVCB substances (Unknown or Variable composition, Complex reaction products or of Biological materials) must be established on the basis of similarities in the structures of the constituents, together with the concentration of these constituents and variability in the concentration of these constituents. Qualitative compositional as well as quantitative characterisation of the individual constituents of these substances must be provided, to the extent that this is measurable (Guidance on IRs and CSA, Section R.6.2.5.5.)

26 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, in your category justification document, 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.

27 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.

28 In the absence of such information on the compositions of the category members, the compositional similarities between the category members cannot be confirmed.

0.1.1.2. Applicability domain of the category

29 A category (grouping) hypothesis should address "the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint" (Guidance on IRs and CSA, Section R.6.2.4.1.). Particularly, "the applicability domain of a (sub)category would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members" (Guidance on IRs and CSA, Section R.6.2.1.2.). Therefore, to reliably predict properties within a category the applicability domain should be described including the borders of the category, for which chemicals the category does not hold and a justification for the inclusion and/or exclusion rules.

30 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, primary 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.

31 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 quantitative variations in the concentrations of pools of constituents in the compositions of the category members.

32 Under these circumstances the boundaries of the applicability domain are not defined and that the borders of the category are not clearly established.

0.1.1.3. Conclusion on the scope of grouping (category)

33 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.

0.1.2. Predictions for toxicological properties

34 You have provided documentation as described under 0.1.1. above.

35 You intend to predict the properties of the Substance from information obtained from the analogue substances, listed above.

36 You provide the following reasoning for the prediction of toxicological properties: you state 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*".

37 You consider the RAAF[2] 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*".

38 You use the following assumptions to support the prediction of properties of your Substance from data for the source substances 1-4:

- 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 due to quick and complete breakdown of the ZDDPs constituents into the neutral form;
- "*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*";

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

- "*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*".

39 To support your hypothesis, you have provided the following information:

0.1.2.1. Toxicokinetic properties

0.1.2.1.1. Hydrolysis and absorption

40 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 constituents also negatively influence their absorption. In addition, "low" absorption is predicted using SwissADME.

41 In the justification document, you claim that the basic form of ZDDPs is "*quickly and completely broken down into the neutral form"*, and "*ZDDP that is soluble in the GI fluid is expected to be hydrolyzed resulting in the dissociation of the Zn from the alkyl dithiophosphate ester moiety"*. Based on this you concluded that "*the amount of basic vs. neutral ZDDP is not relevant for the toxicity assessment as all ZDDPs are expected to be in the neutral form upon ingestion"*.

42 You supported your claim by providing the following information:

- Simulated gastric fluid study (preliminary data), hereafter, referred as study 1, performed with two category members consist of both primary, relatively high initial basic ZDDP (EC 224-235-5) and secondary, relatively low initial basic ZDDP (EC 272-238-5) 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) […]".*

0.1.2.1.2. Metabolism

43 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).

44 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*".

0.1.2.2. Results of toxicity studies

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

46 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 insufficient for assessment*").

47 Further, in the 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).

48 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.

49 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.

0.1.3. ECHA analysis of the prediction of toxicological properties

50 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substances.

51 Specifically, your read across hypothesis is based on:

- structural similarity (core common functionality)
- similar toxicokinetic properties
  - low absorption, the dithiophosphate ester group the only absorbable moiety;
  - similar metabolic pathways
  - common metabolic products
- similar toxicological properties, more specifically lack of systemic toxicity.

52 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.

53 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.3.1. Not sufficient supporting information to compare the toxicokinetic of the category members

54 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of

properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

55 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar category members cause the same type of effect(s), more specifically lack of systemic toxicity. Further, you consider that the only relevant pool is the neutral pool and that the substances in the ZDDP category will have low bioavailability and undergo similar biotransformation to form common metabolic products (DTPE and alkyl alcohols). In this context, relevant, reliable and adequate information characterising the toxicokinetic behaviour of the ZDDP category members as well as the toxicological profile of the common metabolites is necessary to support your hypothesis.

0.1.3.1.1. Hydrolysis and absorption of the ZDDP substances

- Molecular weight

56 You state that the passive absorption of the unchanged constituents is unlikely due to their high molecular weights without any substantiation.

57 However, although increasing molecular weights in general indicate that the likelihood of absorption decreases, you have not provided any substantiation to demonstrate that the molecular weight differences between the individual neutral ZDDP pools can be used to predict differences in absorption for the substances.

- Hydrolysis

58 ECHA understands that you are using the results from the above-mentioned study 1 to support your claims that *"the varying concentrations of basic ZDDP among category members is not relevant"* for the purpose of predicting the toxicological properties of the substances due to its quick and full hydrolysis to the neutral pool. ECHA notes that the study has the following limitations affecting its reliability:

59 First, the composition of the 2 substances tested in study 1 is not reported.

60 This affects the reliability of the information obtained from this study, as reflected in your allocation of a Klimisch score of 4 to this information. Furthermore, the absence of this information in conjunction with the limited characterisation of the compositions of the category members, and in particular the absence of information on the variability in the concentrations of the constituents, does not allow to establish how relevant the information obtained from study 1 is for the other category members. Based on this, you did not demonstrate that the variations in the concentrations of the basic form throughout the category members are not relevant for the purpose of predicting the toxicological properties of the substances.

61 Second, in addition to the quantitative variations in the concentrations of basic ZDDPs, as indicated above, the composition of the members of the category also differs qualitatively. The substances are manufactured from various types of alcohols: primary alcohols, branched chain primary alcohols, secondary alcohols, tertiary alcohols. These variations in the starting materials result in structural variations of the basic ZDDP constituents of the category members. You have not established that the different alcohols (primary (linear or branched), secondary (branched) and mixed) do not influence the conversion of the basic ZDDPs pools or explained how this structural difference would affect the prediction of the toxicological properties of the substances.

62 Based on the above, you have not established that the varying concentrations of basic ZDDP among category members is not relevant.

63 Further, in your justification document you claim that the neutral ZDDP will further dissociate in the gastrointestinal tract (GIT) to the DTPE. ECHA notes that in your dossier you have not provided experimental data to support this claim.

0.1.3.1.2. Metabolism

64 With regards to the biotransformation of the ZDDP category members, 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 has the following observations.

65 Firstly, the prediction indeed identifies potential intermediate metabolites, however, it provides only qualitative but not quantitative information on their formation. Secondly, it has to be noted that any qualitative or quantitative information obtained from predictions has a higher uncertainty compared to information obtained from experimental data.

66 Further, although you acknowledged that it is of great importance to "*[…] understand the toxicity of each biotransformation stage*" you have not elaborated on and accounted for the intrinsic toxicological properties of the intermediate metabolites and on their impact 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.

67 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.

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

0.1.3.2. Missing supporting information to compare the properties of the category members

69 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

70 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar ZDDP category members cause the same type of effect(s). 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".* In this context, relevant, reliable and adequate information allowing to compare the properties of the category members is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

71 First, in support of your hypothesis, you have provided studies on three ZDDP category members with repeated dose administration (as summarized in section 0.1.2.2. above). You have identified the test material by name and CAS/EC number. Even though no detailed information on the composition of the test material is reported, ECHA has analysed the studies, assuming that the test material is representative for the source substances.

72 Effects, such as gastric irritation and submucosal edema (study (ii)), hyperplasia and hyperkeratosis of non-glandular stomach (study (i)) are reported at high doses. You claim that "*all other observations of clinical signs, mortality (both adults and offspring) were secondary to the portal of entry effects*". In addition, the following effects are also reported at the same and/or lower doses as those causing local effects:

- study (i) - 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.
- Studies (ii) and (iii) - changes in weights of organs (adrenal, testes, heart, liver) and neonatal toxicity.
- Study (iv) 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).

73 You have not explained the cause-effect relationship between the gastrointestinal irritation and the effects on organs like adrenal, spleen, testes, liver, brain, as well as on the changes of cholinesterase activity.

74 Without such explanation, it cannot be excluded that the observed effects are signs of treatment-related systemic toxicity, rather than secondary to local toxicity. Therefore, your hypothesis of "complete absence of any evidence of systemic toxicity" is not adequately supported.

75 Second, two category members (test material identified as EC: 230-257-6, EC: 224-235-5) are not skin irritant and 9 are classified as skin irritant. Therefore, you have not provided supporting evidence that all category members have similar toxicity, considering the differences in skin irritation properties.

76 Third, in your read-across justification document, you provide 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*". You also present results from Toxys ToxTracker in vitro mechanistic study in order to demonstrate "*similar biological activity*" of the ZDDP members.

77 However, these considerations do not support your claim, for the following reasons:

- Toxicity of DTPEs

78 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.

79 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. Further, this information is not provided in your registration dossier.

- Toxicity of alcohols

80 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 absence of toxicity.

81 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 prediction.

- Toxicity of base oils

82 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".

83 However, 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*".

84 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 prediction.

- In vitro mechanistic investigations

85 The Toxys ToxTracker in vitro mechanistic 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*".

86 You did not explain how the reported results would support your hypothesis for lack of systemic toxicity. Further, 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.

87 The available set of data on the ZDDP category members does not provide sufficient information to 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.

0.1.3.3. Selection of the source substances to be tested

88 In your testing strategy you have identified four ZDDP category members, as listed above, to be tested in 90-day repeated dose oral toxicity study and pre-natal development toxicity study in one species (rat) to fulfil the standard information requirements of Annex IX, Section 8.6.2. and 8.7.2.

89 Further, in your testing strategy document for the PNDT 2nd species (rabbit) you indicate that "*The preliminary proposal is to test only 2 substances that adequately bracket the variables present – i.e., a ZDDP made from a linear alcohol and a ZDDP made from a branched alcohol*". However, you did not specify the source substances [the test material] you intend to use to predict the properties of your Substance.

90 You justify the selection of the source substances because they "cover and/or bracket" the identified variabilities among the category members, more specifically: molecular weight,

type of starting alcohols, basic vs neutral ZDDP, amount of base oils. Therefore, they are "representative of the sub-categories, and will adequately cover the entire category for subsequent Annex IX and X testing".

91 In Table 2 of your testing strategy, you have summarized how you intend to use the generated experimental data from the 90-day and PNDT in one species toxicity studies to read-across for the other members of the category. You further explain, as an example, that the data to be generated with the source substance EC: 224-235-5, representative for the branched, primary sub-category, will be used to predict the properties for the members in the same sub-category.

92 However, ECHA notes that in the IUCLID dossiers of all category members, including your Substance, you have submitted testing proposals for 90-day study and PNDT study in rat proposed to be conducted with all 4 source substances. This suggests that you intend to use the data obtained from these 4 source substances to predict the properties for all category members.

93 Based on the above, ECHA considers that you did not explain in a clear and unambiguous way how 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.

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

94 In your testing strategy, you have recognized the lack of supporting information, therefore, 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.

95 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 complexity 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 details on the design of the tests that you consider conducting. 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

96 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.

97 In your comments to the draft decision, you agree with ECHA's conclusion that "*there may be insufficient data available to fully support the Category contentions and read-across*". However, you consider that "*the significant amount of new and detailed information which these Annex IX studies (along with all of the preliminary work) may support the similarity of behaviour and hazard potential across the category, or at least allow development of close analogues or sub-groups within which prediction can be supported for read-across*." You further state that "*once the new data is generated, all industry registrants would expect ECHA to consider the implications of these comparable results when looking at the requirements for the Annex X studies (2nd species 414 and OECD 443 EOGRTS) before issuing new Draft Decisions for these*".

98 ECHA acknowledges your statement that the read-across adaptation is currently supported by insufficient data. You have not provided substance-specific arguments and your comment relies on data which are yet to be generated, therefore this does not affect ECHA's assessment and conclusion.

Reasons for the decision(s) related to the information under Annex IX of REACH

1. Sub-chronic toxicity study (90-days)

99 A sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

1.1. Information provided to fulfil the information requirement

100 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 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).

101 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.

102 ECHA received third party information concerning the testing proposal during the third-party consultation.

103 The third party has expressed a support to the testing strategy, proposed by you and putting forward the same arguments that are already addressed in section 0.1. of Reasons common to several requests above.

104 ECHA agrees that a 90-day study is necessary.

1.2. Grouping of substances and read-across approach

105 As explained in section 0.1. of Reasons common to several requests above, your adaptation of the information requirement is not accepted. Hence, there is a need to test the Substance.

1.3. Specification of the study design

106 According to the OECD TG 408, the rat is the preferred species. Therefore, the study must be conducted in the rat.

107 The oral route of administration is the first choice for investigating systemic toxicity (Guidance on IRs & CSA, Section R.7.5.4.3.2.).

1.4. Outcome

108 Your testing proposal is rejected under Article 40(3) (d) of REACH. Under Article 40(3)(c) you are requested to carry out the additional test with the Substance, as specified above.

109 In your comments to the draft decision you, agreed to perform the requested study.

2. Pre-natal developmental toxicity study

110 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

2.1. Information provided to fulfil the information requirement

111 You have submitted a testing proposal for a PNDT study according to 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).

112 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.

113 ECHA received third party information concerning the testing proposal during the third-party consultation.

114 The third party has expressed a support to the testing strategy, proposed by you and putting forward the same arguments that are already addressed in section 0.1. of Reasons common to several requests above

115 ECHA agrees that a PNDT study in a first species is necessary.

2.2. Grouping of substances and read-across approach

116 As explained in section 0.1. of Reasons common to several requests above, your adaptation of the information requirement is not accepted. Hence, there is a need to test the Substance.

2.3. Specification of the study design

117 You may select between the rat or the rabbit because both are preferred species under the OECD TG 414 (Guidance on IRs & CSA, Section R.7.6.2.3.2.).

118 The oral route of administration is the most appropriate to investigate reproductive toxicity (Guidance on IRs & CSA, Section R.7.6.2.3.2.).

2.4. Outcome

119 Your testing proposal is rejected under Article 40(3) (d) of REACH. Under Article 40(3)(c) you are requested to carry out the additional test with the Substance, as specified above.

120 In your comments to the draft decision you, agreed to perform the requested study.

Reasons for the decision(s) related to the information under Annex X of REACH

3. Pre-natal developmental toxicity study

121 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in two species is a standard information requirement under Annex X, Section 8.7.2. to REACH.

3.1. Information provided to fulfil the information requirement

122 In section 7.8.2. of IUCLID you have submitted a testing proposal for a PNDT study in rabbit, according to OECD TG 414 by oral route, but you have not specified test material. Instead, you indicate that "ZDDP category member(s) to be determined based on results of test proposal".

123 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. You also indicated a weight of evidence 'indicating', thus not concluding, unlikely developmental toxicity but also that this indication must be confirmed by the proposed testing proposals. ECHA has taken these considerations into account.

124 ECHA received third party information concerning the testing proposal during the third-party consultation.

125 The third party has expressed a support to the testing strategy, proposed by you and putting forward the same arguments that are already addressed in section 0.1. of Reasons common to several requests above

126 ECHA considers that a study according to the proposed test guideline fulfil this information requirement.

3.2. Grouping of substances and read-across approach

127 As explained in section 0.1. of Reasons common to several requests above, your adaptation of the information requirement is not accepted. Hence, there is a need to test the Substance.

3.3. Specification of the study design

128 Under the OECD TG 414, the rat or the rabbit are the preferred species (Guidance on IRs & CSA, Section R.7.6.2.3.2.). Therefore, a PNDT study according to the OECD TG 414 must be performed in rabbit or rat as the second species, depending on choice of species for the first PNDT study.

129 The oral route of administration is the most appropriate to investigate reproductive toxicity (Guidance on IRs & CSA, Section R.7.6.2.3.2.). Therefore, the study must be conducted using the oral route.

3.4. Outcome

130 Your testing proposal is rejected under Article 40(3) (d) of REACH. Under Article 40(3) (c) of REACH, you are requested to carry out the additional test with the Substance, as specified above.

131 In your comments to the draft decision, you agree with ECHA's assessment that the provided information does not fulfil the information requirement. However, you state that

you "*do not accept the information requirement decision at this time along with the requirements at Annex IX*". In your comments, you indicate an intention to perform a PNDT study in one species first, and then evaluate the need to perform a PNDT study in a second species.

132 PNDT studies 'on one species' and 'in a second species' are standard information requirements under REACH, section 8.7.2 of Annexes IX and X, respectively. The standard information requirement of a PNDT study in a second species can be omitted only if, taking into account the outcome of the first test and all other relevant available data, an adaptation pursuant to REACH Annex X, section 8.7, Column 2 or Annex XI can be justified.

133 ECHA acknowledges your intention to perform these studies sequentially and points out that the indicated deadline allows for sequential testing for PNDT.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

The information requirement for an Extended One-Generation Reproductive Toxicity Study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study are needed for the design of the EOGRTS.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 18 November 2021.

ECHA held a third-party consultation for the testing proposal(s) from 21 December 2021 until 4 February 2022. ECHA received information from third parties (see corresponding Appendix/Appendices)

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

ECHA took into account your comments and did not amend the requests.

Deadline to submit the requested information in this decision

In the comments on the draft decision, you requested an extension of the deadline from 24 to 36 months for the 90-day study and from 36 to 48 months for the PNDT studies, from the date of adoption of the decision. To justify the additional time needed you stated that you like "*to conduct all testing for the substance (and other ZDDP substances for which Draft Decisions have recently been communicated) at the same test laboratory*" in order "*to ensure consistency in study set-up, conduct, evaluation, interpretation, and reporting and also ensures the most efficient use of animals".* In addition, you provided information from a CRO, indicating that based on the current capacity of the laboratory, 42 months are needed to perform and submit the studies.

Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 36 months for the 90-day study and to 48 months for the PNDT studies.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[3].

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

You reported within the joint submission the registered substance Zinc O,O,O',O'-tetrakis(1,3-dimethylbutyl) bis(phosphorodithioate) (EC no: 218-679-9). 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. In addition, base oils are reported as constituents. The base oils are refined crude oils and UVCB substances.

ECHA considers it may be possible that the different possible constituent ratios result in different hazard properties, if tested in toxicity studies.

[3] https://echa.europa.eu/practical-guides

To avoid underestimation of the hazard caused by the inappropriate selection of the test material you 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 neutral tetrabutyl ZDDP and the concentration of the basic tetrabutyl ZDDP and the concentration of the base oils appears to be a relevant consideration.

Information on the Test Material needed in the updated dossier

a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.

b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

c) The reported composition must also include detailed information on the composition of the test material using appropriate analytical techniques. The reporting must include the concentration values of the monomeric neutral tetrakis (1,3-dimethylbutyl) ZDDP, the concentration values of the dimeric neutral tetrakis (1,3-dimethylbutyl) ZDDP, the concentration values of the basic tetrakis (1,3-dimethylbutyl) ZDDP, and the concentrations, identities and compositions of the base oil

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).