SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Phenol, dodecyl-, sulfurized, calcium salts

EC No 272-486-4

CAS No 68855-45-3 / 220794-90-1

Evaluating Member State(s): France

Dated: 1 November 2017

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2016

Member State concluded the evaluation without the need to ask further information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Phenol, dodecyl-, sulfurized, calcium salts (EC No 272-486-4, CAS No 68855-45-3) was originally selected for substance evaluation based on the following initial grounds of concern: Environment/Suspected PBT; Suspected CMR; Exposure/Wide dispersive use; Consumer use; Aggregated Tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Before starting the substance evaluation a final decision on a compliance check to request further information was issued to the lead registrant of Phenol, dodecyl-, sulfurized, calcium salts on 2 September 2015. The data requested by ECHA to clarify the SID was not obtained in sufficient detail from all registrants to fully clarify the composition – and the variability in the composition between registrants - of the registered substance until after the end of the CoRAP year.

Phenol, dodecyl-, sulfurized, calcium salts (EC No 272-486-4, CAS No 68855-45-3) is an UVCB (substance of Unknown or Variable composition, Complex reaction products or Biological materials). In addition to the constituents described in the name of the registered substance, different base oils make part of the composition. The composition of these base oils may vary from one registration dossier to the other.

The registered substance is a calcium salt of sulfurized alkylphenols. However, the composition of the UVCB needed to be clear to define if the information present in the registration dossier (or available in the literature) covers the registered substance, including "worst case constituents", for each endpoint. It should also be taken into account that variations in the composition may exist within the joint submission.

Due to the time required for receiving full clarity on the composition of the registered substance the evaluation has been limited to reviewing the information present in all of the registered dossiers. Based on this evaluation some conclusions on the need for follow-up actions at the EU level were drawn (as further discussed in Section 4). It was however felt that any requirements for new data should be based on an identification of which constituent(s) of the registered substance that is(are) most relevant to address the potential concerns. However, due to the timing of the incoming information, the eMSCA was not able to set up a definitive strategy for information requirements to further evaluate the PBT properties and human health toxicity.

The oil component of the Phenol, dodecyl-, sulfurized, calcium salts composition is included among the substances discussed in the Petroleum and Coal stream Substances (PetCo) Working Group. The working group's primary activity was to develop an approach on how to prioritise and address petroleum and coal stream UVCB substances. Discussions are ongoing on how to address the hazard assessment (e.g. PBT assessment) of those substances in general. The systematic assessment of the prioritised substances will start at a later stage.The three following substances (EC 272-486-4, EC 272-234-3, EC 272-233-8; further details in the table below) belong to the same group of substances (alkylphenols sulphides). They all contain oil and Phenol, dodecyl-, branched (TPP, EC 310-154-3), which itself is on CoRAP 2019 (DE).

Due to the remaining unclarities related to the hazard profile of the Phenol, dodecyl-, sulfurized, calcium salts the eMSCA considers that continuing the assessment of the alkylphenolates may be appropriate, possibly within a category approach including the substances which are currently under discussion for EU-wide risk management measures.

EC#	EC name	Substance evaluation status
272-486-4	Phenol, dodecyl-, sulfurized, calcium salts	SEv concluded (FR)
272-234-3	Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	SEv ongoing (NL)
272-233-8	Phenol, dodecyl-, sulfurized, carbonates, calcium salts	RMOA starting (SE)
310-154-3	Phenol, dodecyl-, branched (TPP)	SEv planned in 2018; Potential endocrine disruptor (DE)

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	RMOA
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	X
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

None on the UVCB substance. See also point 4.1.2 below.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

The classification of the Phenol, dodecyl-, sulfurized, calcium salts as Repr. Cat. 1B, based on the constituent Phenol, dodecyl-, branched (EC No 310-154-3) (also know as Tetrapropenyl phenol or TPP) fulfil the conditions for its identification as an SVHC. Similarly, the three substances (EC 272-486-4, EC 272-234-3, EC 272-233-8) of the same group

(alkylphenols sulphides) also contain oil and TPP (EC 310-154-3). They could also be identified as SVHC. Once substances are included in the Candidate List (i.e. identified as SVHCs), they will be subject to prioritisation for inclusion in Annex XIV (unless the SVHC identification process is used only to conclude on PBT/vPvB/ED properties to support the restriction process and an intention for restriction is notified).

4.1.3. Restriction

This option has not been evaluated but could be addressed within the scope of the RMOA.

4.1.4. Other EU-wide regulatory risk management measures

Identity
The identity and composition of the registered substance is not clear and the sameness of the substance between the different registrants has to be further assessed.

Despite the uncertainties in terms of composition of the substance and sameness between registrants, a constant between the various updates and the data available shows the presence of the constituent TPP (EC number 310-154-3) in the registered substance with a content between 1-9%.

Environment
The evaluation of Environmental fate of Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8 or 220794-90-1) remains preliminary due to the timing of the incoming information related to the composition of the registered substance.

Human Health
The evaluation of Human Health hazard of Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8) remains preliminary due to timing of the incoming information on the composition of the registered substance. Reproductive toxicity is recognized based on harmonized classification of its constituent Phenol, dodecyl-, branched [Tetrapropenylphenol (TPP), *EC no.: 310-154-3*] which is present at a concentration > 0,1 % w/w in the registered substance that triggers classification of the substance, as Repr. Cat. 1B.

The evaluating MSCA notes that the registered substance is considered a CMR substance, by the presence of constituent Phenol, dodecyl-, branched (EC No 310-154-3).

Overall conclusion
The evaluating MSCA concludes not to request further information from the Registrants.

However:
- based on the available information;
- by the fact that Phenol, dodecyl-, sulfurized, calcium salts (EC 272-486-4) belongs to the same group of substance (alkylphenol sulphides) (with the following substances: Phenol, dodecyl-, sulfurized, carbonates, calcium salts EC 272-233-8 and Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (EC 272-234-3));
- Phenol, dodecyl-, branched (EC 310-154-3) is planned to be assessed on a potential endocrine disruptor effects, in 2019;

The eMSCA proposes that a risk management option analysis (RMOA) is conducted to consider whether further risk management measures would be needed, maybe including all the substances of the group.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

/

5.2. Other actions

/

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
RMOA to address e.g. SVHC identification	2019	France together with Sweden and the Netherlands

Based upon the detailed evaluation of available information (registration dossiers, Chemical Safety Reports, other scientific evidence described in studies and literature), the evaluating Member State, FRANCE, was not in the position to clarify all of the concerns based on which the substance was selected for substance evaluation

It could however be established that the substance under evaluation is considered a CMR substance, by the presence of the constituent Phenol, dodecyl-, branched (EC No 310-154-3). Consequently, there is a need to take a follow up action based on this property.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

As mentioned in the justification document, Phenol, dodecyl-sulfurized, calcium salts (EC no. 272-486-4, CAS no.68855-45-3 or CAS no. 220794-90-1) was originally selected for substance evaluation in order to clarify concerns as described below in the CoRAP justification document:

- *" The substance is a potential CMR considering the current self classification identified and the proposal for harmonized classification of one constituent Phenol, dodecyl-, branched [Tetrapropenylphenol (TPP), EC No 310-154-3] which is present in the substance in a concentration range that might trigger classification of the substance.*
- *The substance is a potential PBT :*
  - *P (vP) is met through screening criteria,*
  - *T is met due to the impurity*
  - *the non-B status proposed in the registration data is however questioned due to data lacking and poor quality of the available data and rationale used.*

- *Therefore further information on B is needed. The overall PBT assessment appears to be insufficient (for instance information is lacking and the assessment doesn't address each component individually).*

Besides the high aggregated tonnage, uses appear to be wide dispersive (according to the PROCs described) and several consumer uses were identified by the registrant (probably as a mixture) that may raise a high concern if the substance was to be classified Repr. 1B or 2 because of the pending harmonized classification of its impurity."

Before starting the substance evaluation a decision to request further information was issued on a compliance check of the Phenol, dodecyl-, sulfurized, calcium salts in 2016. The data requested by ECHA to clarify the SID was not obtained in sufficient detail from all registrants to fully clarify the composition of the registered substance until after the end of the CoRAP year.

For this reason the hazard evaluation remains partly preliminary as further described in the following sections.

7.2. Procedure

Based on the findings of the manual screening of Phenol,dodecyl-, sulfurized, calcium salts substance evaluation was justified (Justification for the selection of a candidate CoRAP substance). Substance evaluation started in March 2016.

In February 2017 France informed ECHA that neither a draft decision, nor a Substance Evaluation Report or a Conclusion document could be produced in due time as the missing information on SID. The outcome of substance evaluation was therefore postponed to the 6th of November 2017.

The evaluating MSCA concluded that Phenol,dodecyl-, sulfurized, calcium salts can be identified as a SVHC based on its content of TPP for which classification as Repro 1B has been proposed by RAC.

It cannot at present be concluded if the substance is fulfilling the PBT/vPvB criteria of Annex XIII.

The eMSCA proposes that a risk management option analysis (RMOA) is conducted to consider whether further risk management measures would be needed, maybe including all the substances of the group.

7.3. Identity of the substance

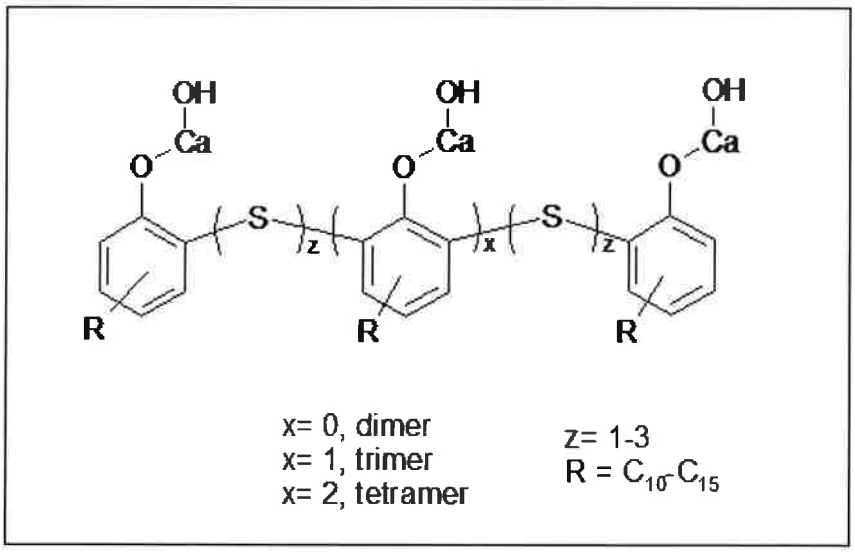
Table 5

SUBSTANCE IDENTITY	
Public name:	Phenol,dodecyl-, sulfurized, calcium salts
Chemical name	It will depend on the identification. The registrant has acknowledged that the current EC name is not appropriate to identify the substance in the registration dossier and is expected to submit a change of identifiers request to ECHA. The appropriate new chemical name will reflect the presence of the oils used by the registrants in the composition of the substance (e.g. "Phenol, paraalkylation products with C10-15 branched olefins (C12 rich) derived from propene oligomerization,

	calcium salts, sulfurized, including [*identity of the oil*]").
EC number:	272-486-4 → will depend on the identification
CAS number:	68855-45-8 / 220794-90-1 → will depend on the identification
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	
Molecular weight range:	→ will depend on the composition and SIP
Synonyms:	

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☒ UVCB

Structural formula:



Multiconstituent/UVCB substance/others

This substance corresponds to a UVCB substance. The composition includes different constituents for which structure may vary in relation to the length of the alkyl chain bound to the aromatic ring. The aromatic rings may be bound one to the other with sulfur bridges forming dimers, trimers and tetramers. In addition, in relation to the sulfurization, constituents may show the presence of different sulfur bridges.

In addition the composition of the registered substance includes the presence of multiple base oils. Clarification on the identity of these base oils was part of the requests made by ECHA in relation to the substance identification.

The compositional information included in all registration dossiers reports also the presence of the alkylphenol starting material, also identified as dodecyl-, branched (TPP, EC 310-154-3) with a concentration between 1 and 9 percent.

7.4. Physico-chemical properties

As there remains uncertainties related to the identity of the registered substance (composition and sameness of the substance between the different registrants), it was not possible to fully assess the physico-chemical properties of "the" substance.

7.5. Manufacture and uses

7.5.1. Quantities

This substance is manufactured and/or imported in the European Economic Area in 1000 - 10 000 tonnes per year.

Table 8

Tonnage range to be ticked only.

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

Two manufacturers of Phenol, dodecyl-, sulfurized, calcium salts worldwide have been identified.

7.5.2. Overview of uses

This substance is used in the following products: lubricants and greases and hydraulic fluids.

This substance is used in the following areas: as an intermediate or extraction agent, formulation of lubricant additives and lubricant, lubricant in vehicles or machinery.

This substance is used for the manufacture of: general professional use of lubricants in vehicles or machinery

Table 9

USES	Use(s)
Uses as intermediate	Manufacture or use as an intermediate or extraction agent PROC: 1, 2, 3, 4, 8a, 8b ERC: 1
Formulation	Uses in industrial formulation of lubricant additives and lubricants. Includes material transfers, mixing, large and

	small scale packing, sampling, maintenance and associated laboratory activities. Uses as such and in a mixture PROC: 1, 2, 3, 4, 5, 8a, 8b, 9, 15 PC: 17, 24, 25 ERC: 2 SU: 10
Uses at industrial sites	Uses in a mixtures In general industrial using of lubricants in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines) PROC: 1, 2, 7, 8b, 9, 10, 13 PC: 17, 24 ERC: 4, 7
Uses by professional workers	Uses in a mixture In general professional using of lubricants in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines) PROC: 1, 2, 7, 8a, 8b, 9, 10, 11, 13, 20 PC: 17, 24 ERC: 8a, 8b, 8d, 9a, 9b
Consumer Uses	General consumer use of lubricants in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines) PC: 24 ERC: 8a, 8d, 9a, 9b
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

None

7.6.2. Self-classification

The registration data includes the following self classification:

- According to CLP criteria:
  - Repr. 1B H360: May damage fertility or the unborn child
  - Aquatic Chronic 4 H413: May cause long lasting harmful effects to aquatic life
- According to DSD criteria:
  - Repr. Cat. 2; R60 May impair fertility
  - R53 May cause long-term adverse effects in the aquatic environment

In addition the following classification(s) are included in the Classification and Labelling Inventory:

- Eye Irrit. 2, H319: Causes serious eye irritation
- Aquatic Chronic 4, H413: May cause long lasting harmful effects to aquatic life
- Repr. 2, H361: Suspected of damaging fertility or the unborn child

7.7. Environmental fate properties

Before starting the substance evaluation a decision to request further information was issued on a CCH of the Phenol, dodecyl-, sulfurized, calcium salts in 2016. The data requested by ECHA to clarify the SID was not obtained in sufficient detail from all registrants to fully clarify the composition of the registered substance until after the end of the CoRAP year.

For this reason the hazard evaluation remains partly preliminary as further described in the following sections.

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

Data waiving

Reason: study scientifically unjustified

Justification: As the registered substance is highly insoluble in water, testing for this endpoint does not need to be conducted under EC Regulation 1907/2006, Annex VIII, Column 2, point 9.2.2.1. According to the EU Directive 67/548/EEC, a poorly soluble substance can be defined as a substance with a solubility of less than 1 mg/L.

Furthermore, the registrant reminded that registered substance is dissolved in base oil and contains a number of components with various numbers of sulphur atoms. The number of components in the product would further reduce the detection levels, make the identification of the hydrolytic products unfeasible and could have different hydrolysis rates.

No information regarding the hydrolysis of the oil components have been provided.

7.7.1.1.2. Phototransformation/photolysis

No information available

7.7.1.1.3. Phototransformation in air

The studies on phototransformation in air are summarised in the following table:

Table 9. Overview of studies on phototransformation in air Method

	Results	Remarks	Reference
REACH guidance on QSARS R.6, 2008 PHOTOCHEMICAL REACTION WITH OH RADICALS - Concentration of OH radicals: 1.5E6 OH/cm3 - 12 hour day Degradation rate constant: 83.3113e-12 cm3/molecule-sec - Computer programme: AOPWIN V1.91 (EPIWIN V3.12) - Other: Half-Life = 1.541 hours	Half-life (DT50): 1.541 h	4 (not assignable) disregarded study (Q)SAR **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts (mono-sulfur)**	USA EPA (2008a)

PHOTOCHEMICAL REACTION WITH OH RADICALS - Concentration of OH radicals: 1.5E6 OH/cm3, 12 hour day - Degradation rate constant: 42.7810 E-12 cm3/molecule-sec - Computer programme: AOPWIN V1.91 (EPIWIN V3.12) - Other: HALF-LIFE = 3.000 Hrs	Half-life (DT50): 3 h	4 (not assignable) disregarded study (Q)SAR **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts (disulfur)**	USA EPA (2008a)

It should be noted that the applied QSARs have not been validated for salts or chemicals that are of variable composition. The composition of this substance comprises a number of molecules of varying structure with a distribution of carbon chain lengths with varying numbers of alkyl-phenol rings and sulfur bridging between those alkyl-phenol rings. As such, the calculated value presented is based upon two theoretical structures, and results are not considered to be representative of the value that would be predicted for the substance as a whole. Moreover, the two tested theoretical structure have not been provided and no assumption regarding the half life of the different structures can be carried out. As such, the estimated value derived from the EPIWIN models have been considered as not reliable.

No information regarding the phototransformation in air of the oils components has been provided.

7.7.1.1.4. Phototransformation

No information available

7.7.1.2. Biodegradation

7.7.1.2.1. Biodegradation in water

7.7.1.2.1.1. Estimated data

No estimated data were provided. Available QSARs have not been validated for salts or chemicals that are of variable composition. The composition of this substance comprises a number of molecules of varying structure with a distribution of carbon chain lengths with varying numbers of alkyl-phenol rings and sulfur bridging between those alkyl-phenol rings. Therefore, different structures should be tested and it should be justified how the chosen structures cover the assessment of the whole substance. Moreover, biodegradation of the constituents of the oils should have been investigated.

7.7.1.2.1.2. Screening tests

The test results are summarised in the following table:

Table 10. Overview of screening tests for biodegradation in water

Method	Results	Remarks	Reference

Test type: ready biodegradability activated sludge (adaptation not specified) EU Method C.4-C (Determination of the "Ready" Biodegradability - Carbon Dioxide Evolution Test)	Not readily biodegradable % Degradation of test substance: 4.7 — 10.8 after 28 d (CO2 evolution)	2 (reliable with restrictions) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts** 60% alkyl phenol sulfide and 40% highly refined lubricant base oil	[redacted] (1996)
Test type: ready biodegradability activated sludge (adaptation not specified) OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test)	Not readily biodegradable % Degradation of test substance: 13.4 after 28 d (CO2 evolution)	2 (reliable with restrictions) key study experimental result Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts 60% alkyl phenol sulfide and 40% highly refined lubricant base oil.	[redacted] (1998)
activated sludge, domestic, non-adapted equivalent or similar to OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test)	% Degradation of test substance: 38.8% after 28 d (CO2 evolution)	4 (not assignable) supporting study experimental result Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts. Oil content not reported	>>>Author missing<<< (2000a)

[redacted], 1996 ([redacted]) conducted a CO2 evolution test on a test substance. This was conducted according to the EU Method C.4-C (Determination of the "Ready" Biodegradability - Carbon Dioxide Evolution Test). In this study, until 10.8% of degradation was measured after 28d. A toxicity control indicated that the tested substance is not toxic for microorganisms (43% of degradation after 28 days). Some information are lacking to validate this study. At first, it was claimed that the validity criteria regarding the degradation of the reference substance was met however it is not reported when the required threshold was reached. Second, the kind of wastewater treated by the plant where the sludge was sampled is unknown whereas the sludge came from a water pollution control center. At last, the inorganic carbon content of the test chemical suspension in the mineral medium at the beginning of the test and the total CO2 evolution in the inoculum blank at the end of the test have not been provided.

A second study on the ready biodegradability of the test substance in a CO2 Evolution Test ([redacted], 1998, [redacted]) was

conducted according to OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test). In this test, 13.4% of degradation was measured after 28d. The number of replicate is not clearly reported and as in the previous study, the inorganic carbon content of the test chemical suspension in the mineral medium at the beginning of the test and the total CO2 evolution in the inoculum blank at the end of the test have not been provided. The validity criteria regarding the degradation of the reference substance is fulfilled.

Finally, supporting information, obtained from the 2000 European Chemicals Bureau IUCLID Data Set for the substance is presented. But no information regarding the material and methods and regarding the validity criteria were reported for the third study.

Despite some information are lacking, two tests indicate that the substance is not readily biodegradable. No further simulation tests are provided. The substance is therefore considered as P/vP based on screening information. As the substance tested in the two ready biodegradation tests contain one oil, the oil could be considered as covered by this tests. However, it should be reminded that two different oils can be added to the alkyl phenolate substances depending on the registrant It is therefore not know if the registered substance is covered by the available tests.

7.7.1.2.1.3. Simulation tests (water and sediments)

Data waiving

Reason: study scientifically unjustified

Justification: In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation. Nevertheless, the risk assessement is at present based on PNEC derived from studies which cannot be validated because of the identity issue. Therefore, this issue could be reassessed if valid ecotoxicity data is available.

7.7.1.2.1.4. Biodegradation in soil

Data waiving

Reason: study scientifically unjustified

Justification: In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation. Nevertheless, the risk assessement is at present based on PNEC derived from studies which cannot be validated because of the identity issue. Therefore, this issue could be reassessed if valid ecotoxicity data is available.

7.7.1.2.1.5. Summary and discussion of degradation

Abiotic degradation

No test data on abiotic degradation is available. This material has very low water solubility, low volatility and is expected to distribute to the sediment or soil compartment. As such, hydrolysis and phototranformation are unlikely to be significant contributors to the environmental degradation of this material.

Biotic degradation

The tested substances are not readily biodegradable based on ready biodegradability studies. Data for degradation in soil or sediment are not available. Such degradation tests would be necessary to conclude on P status of the substance and to determine if relevant degradation products could occur. The substance is therefore considered as P/vP based on screening information. As the substance tested in the two ready biodegradation tests

contained one oil, the oil could be considered as covered by these tests. However it should be reminded that two different oils can be added to the alkyl phenolate substances. It is therefore not known if the registered substance is covered by the available tests.

7.7.2. Environmental distribution

7.7.2.1. Adsorption/desorption

An HPLC adsorption study was carried out on Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (EC 272-234-3) which results from the carbonation of the calcium hydroxide of the Phenol, dodecyl-, sulfurized, calcium salt.
This study on adsorption/desorption is summarised in the following table:

Table 11. Overview of studies on adsorption/desorption

Method	Results	Remarks	Reference
Study type: adsorption (soil/sewage sludge) HPLC estimation method OECD Guideline 121 (Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC))	Adsorption coefficient: log Koc: > 5 at 22 °C (At both pH 2 and 10)	2 (reliable with restriction) key study read-across from supporting substance (structural analogue or surrogate) **Test material (EC name): Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased**	[redacted] (2010)

Discussion

The study was conducted according to OECD Guideline 121, Estimation of the Adsorption Coefficient (KOC) on Soil and on Sewage Sludge using high performance liquid chromatography (HPLC).

At pH values of 2 and 10, the k' for Phenol, dodecyl-, sulfurized, calcium salts could not be calculated for both the 5.0 and 10 mg L^{-1} test concentrations. This was because there were no substantial sample peaks observed in any of the chromatograms. It has been demonstrated that the test substance has a chromophore and therefore is assumed to have been retained on the column and has been assigned a log Koc value of >5.0.

The read across between Phenol, dodecyl-, sulfurized, carbonate calcium salt overbased and Phenol, dodecyl-, sulfurized, calcium salt is mainly based on structural similarities, QSARs, and aquatic toxicity tests which cannot be considered as valid. Indeed, aquatic toxicity tests have been carried out at concentrations highly over the supposed solubility of these substances and without any analysis of these substances in the tests. A better justification would be necessary to support the read across between the two substances, including the impact of the carbonation of the calcium hydroxide function on the adsorption properties.

Besides, this substance is a complex mixture comprising a number of molecules of varying structure with a distribution of carbon chain lengths with varying numbers of alkylphenol rings and sulfur bridging between those alkylphenol rings. Therefore, a range of Koc corresponding to the differents constituents should have been determined for this substance.

It is nevertheless expected that Phenol, dodecyl-, sulfurized, calcium salt will have a high Koc based on available information on Kow (log Kow around 10 according to an experimental study, above 12 according to QSARs). Therefore, once released in the environment, the substance is expected to end up mainly in the soil and sediment compartment.

7.7.2.2. Volatilisation

The studies on volatilisation are summarised in the following table:

Table 12. Overview of studies on volatilisation

Method	Results	Remarks	Reference
Henry's Law Constant (HLC), estimated according to Vapour Pressure divided by water solubility. Vapor pressure: 5.04e-023 mm Hg Water solubility: 7.24e-010 mg/L	Henry's Law constant H: ca. 0 atm m^3/mol	4 (not assignable) disregarded study (Q)SAR **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts**	USA EPA (2008b)

Based on this calculated Henry's Law constant, it is expected that the substance is not volatile. However this calculation is derived from physical chemical properties, which have not been evaluated by the eMSCA.

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

Log Kow has been measured using OECD TG 117 on the whole substance giving Log Kow values of 9.8 and 10.1. The reliability of these results is unclear, due to the presence of mineral oil and lack of clarity on the composition of the test substance. However, this data provide an indication of concern for bioaccumulation potential.

The bioaccumulation properties of the substance is assessed through three studies. The first one is a semipermeable membrane devices test carried out on Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased. In the second one, 15 constituents have been chosen to represent the substance and QSARs have been applied on these constituents to determine the BCF predictions. At last, the key bioaccumulation study from the tetrapropenylphenol dossier has been reported. As these last study has been carefully assessed by UK-CA, this study has not been re-assessed in this document, but the last BCF values which have been growth corrected and lipid normalized, have been reported.

The studies on aquatic bioaccumulation are summarised in the following table:

Table 14. Overview of studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
lipid triolein (predominant lipid in fish/mollusks) aqueous (freshwater) static Total uptake duration: ca. 14 d Details of method: BASIS INFORMATION - Measured/calculated logPow: 6.6 Using Semipermeable Membrane Devices (SPMD) to Estimate Bioconcentration Potential of Petroleum Additives	BCF: 2.2 dimensionless	2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) **Test material (EC name): Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased**	Rausina, G.A, W. R. Biggs, P. M. Stonebraker and E. A. Crecelius. (1996)
Details on estimation of bioconcentration: - BASIS FOR CALCULATION OF BCF - Estimation software: OASIS LMC Catagalogic (v5.11.17) BCF base line model (v.02.09) - Result based on measured Kow of 10.1 - Log BCF = 0.87 - BCF = 7.41	BCF: 7.41 (Log BCF = 0.87)	2 (reliable with restrictions) Supporting study QSAR Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts	[redacted]
Oncorhynchus mykiss aqueous (freshwater) flow-through Total uptake duration: 27 d Total depuration duration: 15 d OECD Guideline 305 (Bioconcentration: Flow-through Fish Test)	**BCF: dimensionless Based on total radioactivity, steady state (Time of plateau: 3 d) ()** <u>Exposure 1.1 µg/L</u> edible fraction: 368 non-edible fraction: 826 non-edible fraction: 671	1 (reliable without restriction) supporting study experimental result Phenol, dodecyl-, branched (Tetrapropenyl phenol; TPP) EC 310-154-3 See summary and discussion for relevance	[redacted] (2006)

EPA OPPTS 850.1730 (Fish BioconcentrationTest)	Exposure 11 µg/L edible fraction: 367 non-edible fraction: 744 non-edible fraction: 613		

Key study:
According to the registrant, the key study (Rausina et al., 1996) is considered to have a reliability of 2 based on criteria of Klimisch, the study being considered as well-conducted despite it is a non-guideline and non-GLP study. In addition, this study is being used as read across from EC 272-234-3.

This test system used Semipermeable Membrane Devices (SPMDs), first developed by the United States Fish and Wildlife Service for field sampling studies assessing environmental contamination. SPMDs are low-density polyethylene tubing, with a pore-size similar to the cell membranes in fish. SPMDs are filled with the lipid triolein, the predominant lipid in fishes, and function as "model fish or molluscs" with selective membranes and lipid reservoirs that concentrate organic compounds from water. The test has been carried out for 14 days. A control without triolein has been performed. Phenanthrene was used as a positive control and results with phenanthrene were compared with experimental data in freshwater and marine molluscs.

Reported results are unfortunately not very detailed. No tested substance was detected into the SPDM when it did not contain triolein. With triolein, the BCF of EC 272-234-3 was determined to be 2.2. For phenanthren BCF was 500 in SPMD system and 46 in fish after 14 days exposure. In molluscs, BCF of phenanthren were 14-16. Therefore phenanthren results indicated that SPMD BCF values could be considered as worst case compared to fish and molluscs BCF values.

However, some important information were missing as the conversion factor between the measurement in SPMD system and the calculated BCF value, and the equilibration time. Moreover, the SPMD method is not relevant when dietary exposure is expected, which is the case for the phenol dodecyl sulfurized calcium salt (low solubility, high Kow). At last, the read across between Phenol dodecyl sulfurized carbonate calcium salt overbased and Phenol, dodecyl-, sulfurized, calcium salt is mainly based on structural similarities, QSARs, and aquatic toxicity tests which cannot be considered as valid. Indeed, aquatic toxicity tests have been carried out at concentrations highly over the supposed solubility of these substances and without any analysis of these substances in the tests. More rationale would be necessary to support the read across between the two substances, including the impact of the carbonation of the calcium hydroxide function on the bioaccumulation properties.

At last, there is no information regarding the content of oil of the tested substance. Only the alkylphenolate was radiolabelled and measured in this experiment. It cannot be excluded that the oil (40% of the substance) contains B/vB constituents. Different oils are added to the alkyl phenolate substances, and these oils have not been assessed for their B properties.

Supporting study 1:
BCF was modelled using LMC OASIS Catalogic (v.5.11.17) BCF base-line (v.02.09) modeling software. This substance is a highly complex mixture comprising a number of molecules of varying structure with a distribution of carbon chain lengths with varying numbers of alkylphenol rings and sulphur bridging between those alkylphenol rings. To better assess the UVCB substance being registered, UVCB G Graph 1.0 was used to create a Generic SMILES to incorporate all variations possible in the UVCB nature of the registered substance (EC 272-486-4). Over 1500 isomers were predicted and a filter was used to reduce the number to a manageable but representative amount of structures to be

predicted by catalogic. The filter option selected was Molecular Weight with 3 intervals in order to separate the isomers based on the amount of sulfur bridging (1-3). Five members were randomly selected from each distribution group for a total of 15 constituents for final modeling.
BCF can accurately be predicted using physical/chemical and molecular properties, including:

- Kow
- Metabolism
- Water solubility
- Molecular size
- Molecular charge

The BCF-base line model incorporates all of these factors after starting with a BCF based on Kow (see figure 1). Based on a Kow of 10.1, the predicted BCF without further modification of EC 272-486-4 was 251. The BCF is then modified based on the factors previously described, reducing the BCF prediction to a final value of 7.41. Specifically, the BCF for the molecules evaluated was further decreased due to low water solubility, large molecular size (exclusion from uptake), and metabolism. The BCF prediction was similar for each of the 15 modeled constituents and exactly the same (7.41) for the final prediction where all modifiers are applied. According to the Registrant, a full description of the model, inputs, and results is reported ofthe QSAR Prediction (QPRF format) attached to the IUCLID endpoint study record, nevertheless, such a report was not found in IUCLID. More information should be provided to validate these results in a weight of evidence approach as the validation range. Additionally, the chosen 15 modeled constituents should be presented and it should be justified why they are representative of the whole substance. For instance lower Kow could be expected for the structure with lower carbon chain lengths, which could lead to higher predicted BCF values.

$$\log BCF = \log\left(\prod_i F_i \frac{K_{OW}{}^{n}}{(aK_{OW}+1)^{2n}} + F_W.F_{WS}\right)$$

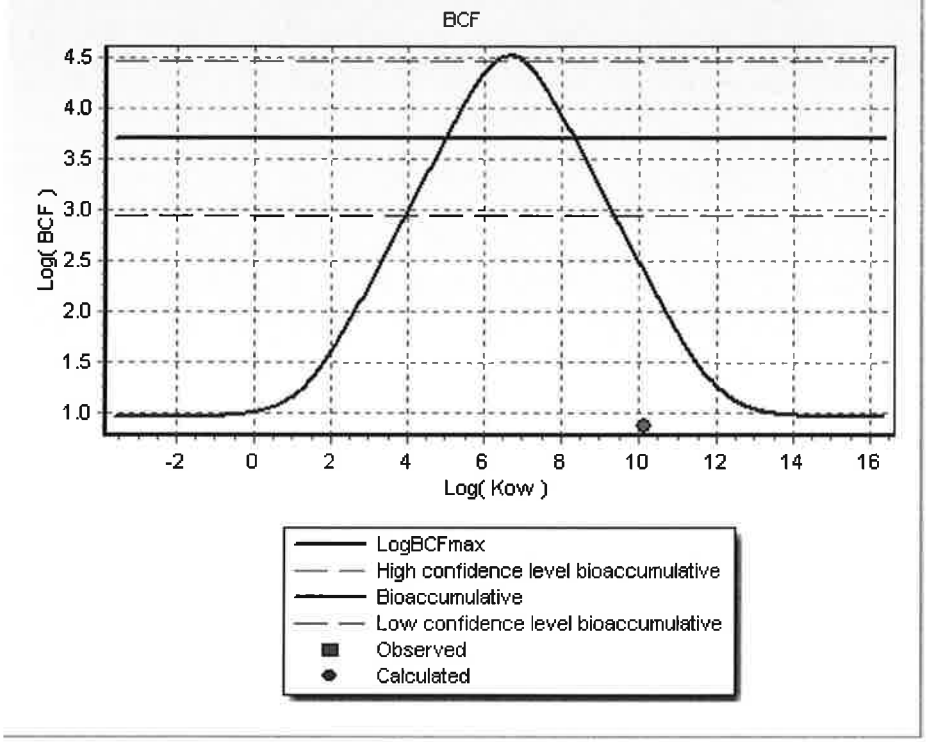


Figure 1. BCF prediction for EC 272-486-4 with all modifiers applied

B assessment of a constituent of the substance (1-9%)

(Supporting study 2)

A Klimisch score 1 guideline and GLP study was conducted with TPP (EC 310-154-3), which is present in the registered substance as a residual impurity/constituent. This constituent is also a precursor of the alkyl phenate sulphide and both substances shared structures similarities. Therefore this study is proposed both as a key study to investigate the B properties of TPP as a constituent of the registered susbtance and as a supporting study for the assessment of the alkyl phenate sulphides, as proposed by the registrant. The BCF value assigned is 826 indicating that **TPP is not B**.

Steady-state TPP concentrations were achieved in the tissues of rainbow trout (*Oncorhynchus mykiss*) after 3 days for both the 1.1 and 11 µg/L treatment groups. Lipid (5%) and growth corrected BCF values based on total radioactivity TPP concentrations were

- 368, 823 and 671 in edible, nonedible and whole fish tissue, respectively, for the 1.1 µg/L treatment group, and
- 367, 744 and 613 in edible, nonedible and whole fish tissue, respectively, for the 11 µg/L treatment group.

Based on TPP chain lengths,,

- BCF were 254 and 267 for the C5 – C10 edible and nonedible fraction, 430 and 385 for the C11 – C12 edible and nonedible fraction, and 582 and 529 for the C13 and greater edible and nonedible fraction, respectively, for the 1.1 µg/L treatment group

- BCF values were 261 and 295 for the C5 – C10 edible and nonedible fraction, 456 and 418 for the C11 – C12 edible and nonedible fraction, and 547 and 509 for the C13 and greater edible and nonedible fraction, for the 11 µg/L treatment group.

Although T (Repro 1B), TPP is not B and therefore neither PBT, nor vPvB.

Based on a comparison of the physical and chemical properties (see table below), alkyl phenate sulfides are expected to less absorbed by fish through aqueous exposure.

	TPP	**Registered alkyl phenate sulfide**
Molecular weight	262.4	667.1-731.2
Water solubility	1.54 mg/L @ 20C	0.082 mg/L @55C
Log Kow	7.14	10.1

Additionnal evidence

A fish dietary bioaccumulation study for the structurally-related substance OLOA 224 (EC 420-470-4) indicates a concern for bioaccumulation potential. However, it has not been assessed in detail whether a read-across between the two substances would be justified. Furthermore, the model and the parameters used to calculate this BCF value are not reported and it is not possible to determine which component(s) of the test material accumulated in the fish.

More details on this study can be found in Annex 3, Confidential Annex.

7.7.3.2. Terrestrial bioaccumulation

No data available.

7.7.3.3. Summary and discussion of bioaccumulation

A weight of evidence approach has been proposed to address the B issue, including

- a semipermeable membrane devices test carried out on Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased as a read across,
- a QSAR on 15 constituents chosen to represent the substance and
- the key bioaccumulation study from the Tetrapropenylphenol dossier.

These data support that Phenol, dodecyl-, sulfurized, calcium salt is not B. Nevertheless, missing data do not allow to validate the semipermeable membrane devices test and a more elaborate rationale should have been provided to support the read across. Information regarding QSAR are not sufficient to validate the results and state that the tested constituents cover the whole alkylphenolate constituents. A valid data indicate that TPP is not B and physical and chemical properties support that phenol dodecyl sulfurized calcium salt should be less absorbed by fish through aqueous exposure.

A fish dietary bioaccumulation study for the structurally-related substance OLOA 224 (EC 420-470-4) indicates a concern for bioaccumulation potential. However, it has not been assessed in detail whether a read-across between the two substances would be justified. Furthermore, the model and the parameters used to calculate this BCF value are not reported and it is not possible to determine which component(s) of the test material accumulated in the fish.

To conclude on alkylphenolates sulphides constituents of the substance, data provided in a weight of evidence approach tend to indicate that these constituents of the registered

substance are not B. Nonetheless, more valid data should have been provided to definitively conclude on the B status.
Most importantly, there is no information regarding the B property of the constituents of the oil and it cannot be excluded that the oil contain B/vB constituents. Two different oils are added to the alkyl phenolate constituents, and these oils have not been assessed for their B properties.

7.8. Environmental hazard assessment

Several acute aquatic toxicity tests have been provided. The content of oil in these tests is not always reported and when it is reported different amounts of oil can occur. Moreover, no information regarding the identity of the added oil are available. Several different oils are added to the alkyl phenolate substances, and it is therefore not possible to state to which extent the provided aquatic toxicity data cover the registered substance.

Before starting the substance evaluation a decision to request further information was issued on a CCH of the Phenol, dodecyl-, sulfurized, calcium salts in 2016. The data requested by ECHA to clarify the SID was not obtained in sufficient detail from all registrants to fully clarify the composition of the registered substance until after the end of the CoRAP year.

For this reason the hazard evaluation remains partly preliminary as further described in the following sections. An assessment of the data of the registration dossier is nevertheless reported below.

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

The results are summarised in the following table:

Table 33. Overview of short-term effects on fish

Method	Results	Remarks	Referenc
ncorhynchus mykiss freshwa ter semi- static OECD Guideline 203 (Fish, Acute Toxicity Test)	LL50 (96 h): > 1000 mg/L test mat. (nominal) NOELR (96 h): 1000 mg/L test mat. (nominal)	1 (reliable without restriction) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts 60% alkyl phenol sulfide and 40% highly refined lubricant base oil.**	[redacted] (1997a)
Cyprinodon variegatus saltwate r semi- static OECD Guideline 203 (Fish, Acute Toxicity Test)	LL50 (96 h): > 10 g/L test mat. (nominal)	1 (reliable without restriction) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts. No information regarding the oil content**	[redacted] (1986)

Pimephales promelas semi-static OECD Guideline 203 (Fish, Acute Toxicity Test)	LC50 (96 h): >= 1000 mg/L test mat. (nominal)	4 (not assignable) supporting study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts**	>>> [redacted] <<< (2000e)
Pimephales promelas static OECD Guideline 203 (Fish, Acute Toxicity Test)	LC50 (96 h): >= 1000 mg/L test mat. (nominal)	4 (not assignable) supporting study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts**	>>> [redacted] <<< (2000f)

In the key study ([redacted] 1997), the acute toxicity of the water accommodated fraction (WAF) of a 1,000 mg/L mixture of the test material and water to the rainbow trout, *Oncorhynchus mykiss*, was investigated during a study which was conducted according to the OECD Guideline 203 (Fish, Acute Toxicity Test) and under GLP conditions. WAFs were prepared at 1,000 mg/L of the test substance in dilution water in a glass mixing vessel equipped with a magnetic stirrer. The mixtures were stirred for approximately 20 hours and allowed to settle for approximately 4 hours. Following the settling period, the water phase containing the WAF was removed from the mixing vessel with a siphon. No insoluble test material was observed in the test vessels during the entire aquatic toxicity test. Test solutions were renewed at 24, 48 and 72 hours. Similar TOC (total organic carbon) were measured in the solutions at 0 and 24 hours in the control and test media. Nevertheless, the active ingredient is in oil and TOC levels are not considered to be indicative of actual test material concentrations. No additional analysis has been carried out and results are therefore based on nominal loading rates. No toxicity was observed in this test. Nevertheless, there is no indication that fish were exposed at all, and if yes to the whole substance or to some of its constituents only. A previous study was carried out by [redacted] in 1993 but was not considered as the key study by the registrant as it was conducted less recently than the above key study. This older study was carried out in the same conditions and with the same substance description on *Pimephales promelas*. Three loading rates were tested (100, 300 and 1000 mg/L). As in the previous test, no toxicity was observed in this test but there is no indication that fish were exposed to whole substance or to some of its constituents only.

[redacted] 1986 study ([redacted]) was conducted under marine conditions. The study was conducted according to the OECD Guideline 203 (Fish, Acute Toxicity Test) and under GLP conditions. The study was therefore considered to have a reliability rating of 1 by the applicant, according to the criteria of Klimisch, 1997. Nevertheless, it should be noted that the oxygen concentration tend to be too low at the end of the test.

Test material was added to a measured volume of water in a glass vessel and stirred for 16 to 20 hours. Following 2 hours of settling, duplicate 20 mL samples were removed for total carbon analysis but data of the analysis were not provided. The water-soluble fraction (WSF) was separated from floating or settled material by gently pumping WSF from a point approximately midway between the bottom, surface and sides of the jar into replica test aquaria. Greater than 90% of the test solution was replaced daily with freshly prepared test solution. The limit test was carried out with a total load of 10 000 mg/L of tested substance, with two replicates. No mortality was observed in the control whereas 5% of mortality was observed for fish exposed to the water-soluble fraction. Nevertheless, without analysis of the tested solutions, it is not possible to state if fish have been exposed to any/ which constituents of the registered susbtance.

Supporting information, obtained from the 2000 European Chemicals Bureau IUCLID Data Set for the substance is presented, however this is a secondary source information and is considered to have a reliability rating of 4.

7.8.1.1.2. Long-term toxicity to fish

Data waiving

Reason: study scientifically unjustified

Justification: The registrant states that, in accordance with column 2 of REACH annex IX, further aquatic toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation. Nevertheless, the chemical safety assessment is based on aquatic toxicity tests which can not be considered as valid. Indeed, available information on tested substance do not allow to warrant that these tests cover the registered substance. Moreover, as the solubility of the substance is low, water accommodated fraction tests have been carried out. No toxicity is observed in these tests however as no analysis of the substance has been carried out, it is not known if the aquatic organisms have been exposed to any constituents of the registered substance.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The results are summarised in the following table:

Table 34. Overview of short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference

Daphnia *magna* freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EL50 (48 h): > 1000 mg/L test mat. (nominal) based on: mobility NOELR (48 h): < 100 mg/L test mat. (nominal) based on: mobility	1 (reliable without restriction) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts :** **75% alkyl phenol sulfide and 25% highly refined lubricant base oil.**	[redacted] (1993)
Daphnia *magna* freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EL50 (48 h): > 1000 mg/L test mat. (nominal) based on: mobility NOELR (48 h): 1000 mg/L test mat. (nominal) based on: mobility	1 (reliable without restriction) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts 75% alkyl phenol sulfide and 25% highly refined lubricant base oil.**	[redacted] (1997)

Crangon crangon saltwate r semi- static Guidelines Issued by the Ministry of Agriculture, Fisheries and Food, Burnham-on-Crouch, Essex England.	LC50 (96 h): > 100 mg/L test mat. (nominal) based on: mortality	3 (not reliable) supporting study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts**	[redacted] (1988)

In the key study ([redacted] 1993), the acute toxicity of the water accommodated fraction (WAF) of five mixtures of the test material and water to the daphnid, *Daphnia magna*, was investigated during a study conducted at [redacted]. The test, which was designed to determine the toxicity of the test substance, was conducted according to the OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test). According to the registrant, the reliability index rating for this study is 1, according to the criteria of Klimisch, 1997 and was chosen by the registrant as the key study based on the worst case scenario result seen, as even though the EL50 was comparable to the [redacted], 1997 study, the NOELR was lower (100 mg/L).

Three WAFs loading rates (100, 300, 1000 mg/L) were prepared by combining the appropriate amount of test substance and dilution water in a glass mixing vessel equipped with a magnetic stirrer and stirring these mixtures for approximately 24 hours, settling the mixtures for approximately 1 hour, and siphoning the water phase containing the WAF. No insoluble material was noted in any test vessels. Similar TOC were measured in the solutions at 0 and 48 hours in the control and test media. Nevertheless, the active ingredient is in oil and TOC levels are not considered to be indicative of actual test material concentrations. No additional analysis has been carried out and results are therefore based on nominal loading rates. At 48-hours, 0, 10, 15, and 25% immobilization were reported for control, 100, 300, and 1,000 mg/L, respectively. These results indicate that daphnia have been exposed to constituents of the tested substance. Nevertheless, **tested substance contained less oil (25%) than the registered substance (40%) and available information do not allow to state that the oils of the tested and of the registered substance are the same or are equivalent**.

The [redacted] 1997 study was not considered as the key study although it is considered of comparative reliability, and was conducted more recently. The above mentionned key study has a lower NOELR and so is considered by the registrant to be the worst case scenario and therefore has been used as the key study. The [redacted], 1997 study was conducted according to the OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) and under GLP conditions and was considered to have a reliability rating of 1, according to the criteria of Klimisch, 1997. Five loading rates were tested 130, 220, 360, 600, and 1000 mg/L. Each of the five WAFs was prepared by combining the appropriate amount of test substance and dilution water in a mixing vessel equipped with a small magnetic stirrer, stirring these mixtures for approximately 20 hours, settling the mixtures for approximately four hours, and siphoning the water phase containing the WAF. As in the previous test, similar TOC were measured in the solutions at 0 and 48 hours in the control and test media. Nevertheless, the active ingredient is in oil and TOC levels are

not considered to be indicative of actual test material concentrations. No additional analysis has been carried out and results are therefore based on nominal loading rates.

No toxicity was observed in this test. Nevertheless, without analysis of the tested solutions, it is not possible to state if daphnia have been exposed to constituents of the registered susbtance. Moreover tested substance contained less oil (25%) than the registered substance (40%) and available information to do not allow to state that the oils of the tested and of the registered substance are the same or are equivalent.

[redacted] 1988 study (HRC report number: [redacted]) was considered to be unreliable by registrant. The study was conducted under marine conditions which are not the preferred conditions for this endpoint and the test solution is considered to have been improperly prepared. Indeed the test substance formed a very poor dispersion in the water column and adhered to the mesh screens around the propeller shield. A small number of globules of the test substance were observed circulating in the water. As such, the study has been assigned a reliability rating of 3.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

Data waiving

Reason: study scientifically unjustified

Justification: In accordance with column 2 of REACH annex IX, further aquatic toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation. Nevertheless, the chemical safety assessment is based on aquatic toxicity tests which can not be considered as valid. Indeed, available information on tested substance do not allow to warrant that these tests cover the registered substance. Moreover, as the solubility of the substance is low, water accommodated fraction tests have been carried out. No toxicity is observed in these tests however as no analysis of the substance has been carried out it is not known if the aquatic organisms have been exposed to constituents of the registered substance. Moreover according to the column 2 of Reach annex VII, **the long-term aquatic toxicity study on Daphnia shall be considered if the substance is poorly water soluble which is the case of the registered substance**.

7.8.1.3. Algae and aquatic plants

The results are summarised in the following table:

Table 35. Overview of effects on algae and aquatic plants

Method	Results	Remarks	Reference

Selenastrum capricornutum (new name: Pseudokirchnerella subcapitata) (algae) freshwat er static OECD Guideline 201 (Alga, Growth Inhibition Test)	EL50 (96 h): > 1000 mg/L test mat. (nominal) based on: growth rate EL50 (96 h): > 1000 mg/L test mat. (nominal) based on: cell number NOELR (96 h): 220 mg/L test mat. (nominal) based on: growth rate NOELR (96 h): 360 mg/L test mat. (nominal) based on: cell number	1 (reliable without restriction) key study experimental result Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts **60% alkyl phenol sulfide and 40% highly refined lubricant base oil.**	[redacted] [redacted] (1997b)
Selenastrum capricornutum (new name: Pseudokirchnerella subcapitata) (algae) freshwat er static OECD Guideline 201 (Alga, Growth Inhibition Test)	NOELR (96 h): 1000 mg/L test mat. (nominal) based on: growth rate EL50 (96 h): > 1000 mg/L test mat. (nominal) based on: growth rate EL50 (96 h): > 1000 mg/L test mat. (nominal) based on: cell number	1 (reliable without restriction) supporting study experimental result Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts **60% alkyl phenol sulfide and 40% highly refined lubricant base oil.**	[redacted] (1994)

In the key study, the acute toxicity of the water accommodated fraction (WAF) of five mixtures of the test material and water to the *Selenastrum capricornutum*, was investigated. The test, which was designed to determine the toxicity of the test substance, and was conducted according to OECD Guideline 201 (Alga, Growth Inhibition Test). Five loading rates (130, 220, 360, 600, and 1,000 mg/L) were prepared by combining the appropriate amount of test substance and dilution water in a mixing vessel equipped with a magnetic stirrer and stirring these mixtures for approximately 20 hours, settling the mixtures for approximately four hours, and siphoning the water phase containing the WAF. Total organic carbon was measured but results of these analyses are not reported in the

IUCLID file. This study is presented as the key information with a reliability rate of 1, however, during the test, the pH range was over 1.5.

No details on the algual cell density are provided but the NOERL of 360 mg/L based on number of cells and the NOERL of 220 mg/L based of specific growth rate indicate that **some toxicity occurred** and thus that algae have been exposed to constituents of the tested substance.

The supporting study ([redacted] 1993 study) was conducted on *Selenastrum capricornutum* according to the OECD Guideline 201 (Alga, Growth Inhibition Test) and under GLP conditions. This study was considered to have a reliability rating of 1 by the registrant, despite a high pH variations during the test. Five loading rates (125, 250, 500, 600, and 1,000 mg/L) were prepared by combining the appropriate amount of test substance and dilution water in a mixing vessel equipped with a magnetic stirrer and stirring these mixtures for approximately 24 hours, settling the mixtures for approximately one hour, and siphoning the water phase containing the WAF. At the beginning and at the end of the test, TOC measurements were non-detected (<1.0 mg/L) in control and 125 mg/L and were detected at 2.0 mg/L at 1,000 mg/L. The active ingredient is in oil and TOC levels are not considered to be indicative of actual test material concentrations. No additional analysis has been carried out and results are therefore based on nominal loading rates.

No toxicity was observed in this test nevertheless, without analysis of the tested solutions, it is not possible to state if algae have been exposed to any constituents of the registered substance and if yes to which.

7.8.1.4. Microbiological activity in sewage treatment systems

Table 39. Overview of effects on micro-organisms

Method	Results	Remarks	Reference
activated sludge, domestic freshwater static OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test)	NOEC (3 h): 1000 ppm test mat. (meas. (not specified)) based on: respiration rate EC50 (3 h): > 10000 other: test mat. (meas. (not specified)) based on: respiration rate	2 (reliable with restrictions) key study experimental result **Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts** **No information regarding the oil content**	[redacted] (1995)
No data OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test)	EC50 (3 h): > 10000 mg/L test mat. (nominal) based on: respiration rate	4 (not assignable) supporting study experimental result	[redacted] (1994)

		Test material (EC name): Phenol, dodecyl-, sulfurized, calcium salts **No information regarding the oil content**	

In the key study, the acute toxicity of the test material activated sludge (domestic) was investigated. The study was conducted according to OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test). Five concentrations were tested (measured concentrations 1.6, 10.6, 103.2, 1040, 10000 mg/L). At the concentration of 10,000 ppm, slight inhibition (26%) of the microbial respiration was observed. This study is presented by the registrant as the key information with a reliability rating for this study is 1.

The supporting study ([redacted] 1994) was conducted according to the OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) and under GLP conditions. However, as only a summary was available, it was considered to have a reliability rate of 4. The respiration rates of the sludge-associated microbes exposed to the five concentrations of the test material (1, 10, 100, 1000, 10000 mg/L) were 39.7, 43.5, 37.7, 44.4 and 33.1 mg O2/L hr respectively. The respiration rate in the control was 44.6 mg O2/L hr. The EC50 was calculated to be greater than 10,000 mg/L.

7.8.1.5. Sediment organisms

Data waiving

Reason: study scientifically unjustified

Justification: In accordance with column 2 of REACH annex X, sediment toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation.

Nevertheless, the chemical safety assessment for the sediment is based on equilibrium partitioning method PNEC, which is derived from aquatic toxicity tests which can not be considered as valid. Indeed, available information on tested substance do not allow to conclude if these tests cover the registered substance. Moreover, as the solubility of the substance is low, water accommodated fraction tests have been carried out. No toxicity is observed in several of these tests and as no analysis of the substance has been carried out, it is not known if the aquatic organisms have been exposed to any/ which constituents of the registered substance.

7.8.2. Terrestrial compartment

Data waiving

Information requirement: Toxicity to soil organisms

Reason: study scientifically unjustified

Justification: In accordance with column 2 of REACH annex IX, short-term terrestrial toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation.

Nevertheless, the chemical safety assessment for the soil is based on equilibrium partitioning method PNEC, which is derived from aquatic toxicity tests which can not be considered as valid. Indeed, available information on tested substance do not allow to conclude if these tests cover the registered substance. Moreover, as the solubility of the substance is low, water accommodated fraction tests have been carried out. No toxicity is observed in several of these tests and as no analysis of the substance has been carried out, it is not known if the aquatic organisms have been exposed to constituents of the registered substance.

7.8.3. Conclusions for environmental classification and labelling

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7.9. Human Health hazard assessment

The evaluation of Human Health hazard of Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8) remains preliminary due to late the timing of the incoming information related to the identity composition of the registered substance. Reproductive toxicity is recognized based on harmonized classification of its constituent Phenol, dodecyl-, branched [Tetrapropenylphenol (TPP), *EC no.: 310-154-3*] which is present at a concentration > 0,1 % w/w in the substance that triggers classification of the substance, as Repr. Cat. 1B.

7.9.1. Toxicokinetics

Not evaluated.

7.9.2. Acute toxicity

Not evaluated.

7.9.3. Irritation

Not evaluated.

7.9.4. Sensitization

Not evaluated.

7.9.5. Repeated dose toxicity

Not evaluated.

7.9.6. Mutagenicity

Not evaluated.

7.9.7. Carcinogenicity

Not evaluated.

7.9.8. Toxicity to reproduction (effects on fertility and developmental toxicity)

Phenol, dodecyl-, sulfurized, calcium salts (EC No 272-486-4, CAS No 68855-45-3) contains in its registered composition in CSR 2016 a percentage of Phenol-dodecyl-branched (TPP) (CAS 121158-58-5, EC 310-154-3) between 2.5% and 9%. TPP is also a residual substance during manufacturing process. An harmonized classification Repr. 1B; H360F (CLP) for TPP (ATP 9) has been adopted by RAC in December 2013 based on the reproductive effects observed in experimental studies in rats. **Therefore considering the presence of TPP in composition of the registered substance with a SCL > 0.3% (according CLP criterias) a classification Repr. 1B ; H360F (CLP) for Phenol, dodecyl-, sulfurized, calcium salts (EC No 272-486-4, CAS No 68855-45-3 / 220794-90-1)** can be proposed. The experimental studies which supported the classification Repr. 1B; H360F for TPP are described below.

Data relevant to assessment of reproductive function and development were evaluated and compared to the classification criteria for reproductive toxicity as described within the CLP Regulation. Data were derived from reproduction, developmental toxicity, and repeated exposure toxicity tests conducted with TPP. Other relevant, supporting information was available from mechanistic studies summarized in Section 7.9.4.3. Based upon all relevant information, the evidence supported the following classification under the CLP regulation:

- **Toxicity to reproduction – fertility: Repr. 1B (May damage fertility)**
- **Toxicity to reproduction – development: Not classified**

A summary of RAC Opinion 2013 on toxicological profile of TPP (RAC opinion 2013) is in Annex 1. Details of the studies are in annex 1 – background document to RAC opinion on phenol, dodecyl-, branched, TPP.

Multiple test results indicate clear, reproducible and consistent adverse effects of TPP on the reproductive system in rats with the potential for relevance of these effects to humans. The weight of evidence from these findings supports a classification for TPP of:

- Category 1B, Presumed Reproductive Hazard to Humans, according to the Classification, Labeling and Packaging Regulation (CLP).

- No classification is proposed for developmental effects.

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated.

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Not evaluated.

7.9.11. Conclusions of the human health hazard assessment and related classification and labelling

Evaluating alkyl phenate sulfides as a category is appropriate based on similar chemical structures, manufacturing processes, physical and chemical properties, functional uses as a lubricating oil additive, and toxicological data. The alkyl phenate sulfide category has been extensively evaluated by regulatory authorities, including:

- OECD SIDS Initial Assessment Report (SIAR). Final assessment report for Alkylphenate sulphides. SIAM 28. 15-17 April 2009. UK/ICCA. http://webnet.oecd.org/hpv/UI/SIDS_Details.aspx?id=5e84eec2-4185-44af-bd86- 72b2aa83fe22

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A summary conclusion of the SIAR 2009 for the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category is in annexe 2 (OECD SIDS 2009).

- Australian Government (NICNAS) IMAP for Long Chain Calcium Phenol Derivatives (http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment- report?assessment_id=130)

The toxicological profile of combined alkyl phenol sulphides and alkyl phenatesulphides (from OECD SIDS SIAR for SIAM 28 Paris, France, April 15-17, 2009 by United Kingdom) is summarized in annexe 2. The quality of the studies used for read-across were evaluated and a Klimish score was attributed for each of them. The data available can be used for the evaluation of Phenol dodecyl sulfurized calcium salts (CAS : 220794-90-1, EC : 272-486-4). This category is composed of four substances covering nine CAS numbers. The CAS numbers of the SIAR dossier 2009 for Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide fit with the CAS number 68855-45-3 registered for the Phenol Dodecyl sulfurized calcium salts dossier and described in the CSR submitted in 2016.
Regarding the Read-Across Assessment Framework (2015), the alkyl phenate category and the substances included in it fit into Scenario 6 (Different compounds have qualitatively similar properties. No relevant variations in properties observed among source substances and the same strength predicted for the target substance).
Adequate, reliable studies on all mammalian toxicity endpoints required under REACH with members of the category have been conducted for dodecyl phenol and for other alkyl phenol sulphides.

Members of this category caused the effects listed below in animal studies, but the relevance of these findings to humans is not known (OECD SIDS SIAR 2009).

Based on read-across with alkyl phenate category the conclusion concerning the following endpoints (acute toxicity, skin and eye irritation, skin sensitization, repeated dose toxicity, mutagenicity, carcinogenicity) are:

- a low concern for acute toxicity by the oral or dermal route of exposure; signs of toxicity and mortality occur at very high dose levels that are much greater than typical human exposure;.
- not irritating to eyes or skin;
- not skin sensitizers;
- a low concern for repeated-dose systemic toxicity up to the oral limit dose of 1000 mg/kg/day;
- not mutagenic *in vitro*;
- a low concern for clastogenicity;
- a low concern for carcinogenicity.

Concerning the endpoints for reproduction, the reproductive and development toxicity data and repeated-dose toxicity data available in the RAC dossier of 2013 for TPP allow the following conclusions:

- a low concern for developmental toxicity;

- a high concern for reprotoxicity due to presence of TPP in substance composition (SCL > 0.3% (according to CLP criteria));
- classification as Repr. 1B H360F (CLP) for TPP.

Based on read across members of the category Alkyl phenate sulfides and alkyl phenol sulfides cause:

- a reduction in fertility in males and females and a reduction in mean live litter size in rats that may be dependent on the concentration of residual TPP + CaTPP present as an impurity;
- a reduction in the size of male and female reproductive organs in rats that may be dependent on the concentration of residual TPP + CaTPP present as an impurity.

Therefore, a classification as Repr. 1B H360F (CLP) is proposed for the Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8).

7.10. Assessment of endocrine disrupting (ED) properties

No evaluation of the endocrine disrupting properties of Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8) has been performed. It should be noted that the ED properties assessment of TPP will be evaluated within the CoRAP in 2018.

7.11. PBT and VPVB assessment

The tested substances in the technical dossier are not readily biodegradable based on ready biodegradability studies. Data for degradation in soil or sediment are not available. The substance is therefore considered as P/vP based on screening information. More data regarding degradation in environmental compartments could be required to definitively conclude on the P status. Moreover, such degradation tests would be necessary to determine if relevant degradation products could occur. As the substance tested in the two ready biodegradation tests contained one type of oil, this oil could be considered as covered by these tests. However, multiple oils with different EC numbers are part of/ used for synthesizing the alkyl phenolate substances. Due to the timing of the incoming information on the substance identification of the oils the eMSCA was not able to evaluate them. It is therefore not known if the registered substance is fully covered by the available tests.

There is no information regarding the B properties of the constituents of the oil and it cannot be excluded that the oil contain B/vB constituents. Due to timing of the incoming information on the substance identification of the oils the eMSCA was not able to evaluate them. Hence, the B properties of the oils have not been assessed.

Regarding the alkyl phenolate part of the substance, a weight of evidence approach is proposed to address the B issue, based on three different studies. The first one is a semipermeable membrane devices test carried out on Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased, as a read across. The second is a set of QSAR performed on 15 constituents chosen to represent the substance. The third one is the key bioaccumulation study from the tetrapropenylphenol dossier. These data support that phenol dodecyl sulfurized calcium salt is not B. Nevertheless, missing data do not allow to validate the semipermeable membrane devices test and a more elaborate rationale should have been provided to support the read across. Information regarding QSAR are not sufficient to validate the results and state that the tested constituents cover the whole alkylphenolate constituents. A valid fish bioaccumulation test indicates that TPP is not B and physical and chemical properties support that phenol dodecyl sulfurized calcium salt should be less absorbed by fish through aqueous exposure. In contrast, a fish dietary

bioaccumulation study for the structurally-related substance OLOA 224 (EC 420-470-4) indicates a concern for bioaccumulation potential. However, it has not been assessed in detail whether a read-across between the two substances would be justified.

To conclude on the alkylphenolates part of the substance, data provided in a weight of evidence approach tend to indicate that these constituents of the registered substance are not B. Nonetheless, more valid data should have been needed to definitively conclude on their B status.

Several acute aquatic toxicity tests have been provided in the technical dossier. Available information on the tested substances do not allow to conclude if these tests fully cover the registered substance. The content of oil in these tests is not always reported and when it is reported, different amounts of oil are found. Moreover, no information regarding the identity of the oil used in the aquatic tests is available. It is therefore not possible to state to which extent the provided aquatic toxicity data cover the registered substance. Besides, as the solubility of the substance is low, water accommodated fraction tests have been carried out but without analysis of the tested substance. In several tests, no toxicity is observed. However, as no analysis of the substance has been carried out it is not known if the aquatic organisms have been exposed to constituents of the registered substance. When toxicity is observed, it indicates that aquatic organisms have been exposed to constituents of the tested substance, but it can not be elucidated if the exposure was to the alkyl phenolate constituents or to the oils constituents. It is therefore difficult to conclude on the T criterion based on these studies.

To conclude, the registered substance can be considered as P/vP based on screening studies. Further degradation tests would be necessary to determine if relevant degradation products are formed. Data provided on the alkylphenolate constituents of the substance tend to indicate that these constituents of the registered substance are not B based on a weight of evidence approach. Nonetheless, more valid data should have been needed to definitively conclude on the B status of these constituents. Besides, there is no information regarding the B property of the constituents of the oils and it cannot be excluded that the oil(s) contain(s) B/vB constituents. Finally, available aquatic toxicity data do not allow to conclude on the T criterion.

FR-MSCA therefore advises to consider continuing the PBT assessment of the alkylphenolates with a category approach including similar substances which are presently under discussion for EU-wide risk management measures. That might probably be through the identification of worse-case constituents of this and similar UVCBs. It should be noted that the used oils are under assessment by the PetCo group, but to our knowledge there is at present no clear status on the oil assessment.

7.12. Exposure assessment

No assessment of exposure of human and environment to Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8 or 220794-90-1) has been performed.

7.13. Risk characterisation

A final characterisation of risks for human and environment of Phenol, dodecyl-, sulfurized, calcium salts dossier (EC 272-486-4, CAS 68855-45-8 or 220794-90-1) has not been performed due to the remaining unclarity of the substance identity.

7.14. References

Studies referred to in the document can be found on ECHA dissemination site:

https://echa.europa.eu/registration-dossier/-/registered-dossier/13858

7.15. Abbreviations

BCF	Bioconcentration Factor
CCH	Compliance Check
CLP	Classification, Labelling and Packaging of substances and mixtures
CMR	Carcinogenic, Mutagenic, Toxic for reproduction
CoRAP	The Community Rolling Action Plan
eMSCA	Evaluating Member State Competent Authority
ED	Endochrine Disruptor
EL50	Half Maximal Effect Loading Rates
ERC	Environmental Release Category
GLP	Good Laboratory Practice
LC50	Median Lethal Concentration
NOEC	No Observed Effect Concentration
NOELR	No Observed Effect Loading Rates
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
PC	Chemical Products Category
PetCo	Petroleum and Coal stream substances
PNEC	Predicted No Effect Concentration
PROC	Process Category
QSAR	Quantitative Structure-Activity Relationship
RAC	Committee for Risk Assessment
RMOA	Risk Management Option Analysis
SEv	Substance Evaluation
SIAR	SIDS Initial Assessment Report
SID	Substance Identity

SIDS	Screening Information Dataset (OECD profile document for a chemical)
SIP	Substance Identity Profile
SU	Sectors of Use
SVHC	Substances of Very High Concern
TOC	Total Organic Carbon
TPP	Phenol, dodecyl-, branched; Tetrapropenylphenol
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
vPvB	Very Persistent and Very Bioaccumulative
WAF	Water Accommodated Fraction
WSF	Water-Soluble Fraction

Annex 1 : RAC Opinion December 2013 on toxicological profile of TPP (RAC opinion 2013).

Summary of the classification justification

Classification for Repr. 1B, H360F according to the CLP Regulation, and Repr. Cat. 2: R60 according to DSD is supported when there is clear evidence from animal studies of an adverse effect of the substance on ***sexual function and fertility*** occurring together with other toxic effects, but where the adverse effects on fertility are not considered to be secondary non-specific consequences of other toxic effects. Considering these criteria, classification as Repr. 1B; H360F (CLP) (Repr Cat. 2; R60, DSD) is justified for TPP based on the following effects observed in experimental studies:

- Reduced epididymal sperm count and prolongation of oestrous cycle at a dose of 75mg/kg in the two-generation reproductive study in rats (Edwards *et al.*, 2012).
- Reduced number of pups born in the F2a generation exposed to a dose of 75mg/kg(Edwards *et al.*, 2012).

- Reduced proportion of animals copulating when cohabited, reduced litter size, alterations in number of corpora lutea, prolongation of oestrous cycle and reduced epididymal sperm count in animals exposed at 125 mg/kg in the one-generation study in rats (Knapp, 2006).

- Acceleration of sexual maturation in female animals that is reported in the two-generation study and in the female pubertal assays.

- The mechanistic information further suggests that TPP has weak estrogenic and androgenic activity.

Impaired fertility has also been observed in the two-generation study in which a chemical mixture of unknown composition but containing TPP was given by gavage to rats at a dose of 67 mg TPP/kg bw/day (Nemec *et al.*, 1995). The pregnancy index was reduced in the F0 and F1 generations in the two-generation study in which a preparation containing TPP was given by gavage to rats at a dose of 38 mg/kg bw/day (Wood *et al.*, 2002). However, the unknown composition of the mixtures tested in these studies makes these results uncertain.

The effects observed in the two-generation and one-generation studies with TPP may be related to an estrogenic action of TPP which has been shown in uterotrophic bioassays in rats (Edwards *et al.*, 2010a and 2010b), and in female pubertal assays in rats (Knapp, 2007a, 2007b, 2009a and 2009b). TPP is also considered as a substance interacting with the ER based on results of the *in vitro* rat uterine estrogen receptor competitive binding assay (Thomas *et al.*, 2012b). Based on the *in vitro* rat prostate androgen receptor competitive binding assay (Thomas *et al.*, 2012a) TPP is considered an AR binder. The binding affinity of TPP was similar to the weak positive control, dexamethasone.

Calculation of a concentration limit for reproductive toxicity

A proposal for the setting of an SCL for TPP was made by Chevron Oronite SAS, but it was not calculated according to the Guidance on the Application of the CLP Criteria. RAC therefore recalculated the proposed concentration limit in accordance with this guidance (version 3.0 – November 2012; point 3.7.2.5); see below.

Determination of the ED_{10} using the available data

The available data from animal studies were evaluated to establish the reproductive toxicity dose descriptor, ED_{10} (effective dose with a 10% effect level above the background/control group), as described below.

ED_{10} based on a 10% reduction in pups body weight

Table 8. Data from the two-generation study (Edwards et al., 2012)

Offspring of F0 females	Dose level (mg/kg bw/day)			
	0	1.5	15	75
Pup Weight (M/F) – PND 7	16.5/15.7	16.1/15.3	15.1*/14.4**	14.3**/13.5**
Pup Weight (M/F) – PND 14	30.1/29.2	30.1/29.1	28.6/27.3	22.9**/21.8**
Pup Weight (M/F) – PND 21	50.7/49.3	49.1/46.8	47.0/45.0*	36.4**/34.4**

*Statistical significance: *p<0.05; **p<.001*

In the two-generation study by Edwards *et al.* (2012) TPP induced reduction in the body weight of pups during lactation. A 10% reduction, compared to controls (16.5 g), of body weight of male pups on PND 7 gives a value of 14.85 g. Interpolation between 15 and 75 mg/kg bw/day to a dose level which would be expected to result in a male pup body weight of 14.85 g gives a value of 33.75 mg/kg bw/day.
(Calculations: (75 – 15)/(15.1-14.3) = 60/0.8= 75; 15.1 – 14.85= 0.25; 0.25 x 75 = 18.75; 15 + 18.75 = 33.75 mg/kg bw/day)
Female pups on PND 21:
A 10% reduction compared to the control body weight (49.3 g) of female pups on PND 21 gives a value of 44.37 g. Interpolation between 15 and 75 mg/kg bw/day to a dose level which would be expected to result in a male pup body weight of 44.37 g gives a value of 18.57 mg/kg bw/day.
(Calculations: (75 – 15)/(45.0 - 34.4) = 60/10.6 = 5.66; 45.0 – 44.37 = 0.63; 0.63 x 5.66 = 3.57; 15 + 3.57 = 18.57 mg/kg bw/day).

ED_{10} based on 10% reduction in ovary weight

Table 9. Data from the one-generation study (Knapp *et al.*, 2005)

Organ/tissue	Weight	Dose level (mg/kg bw/day)			
		0	5	25	125
Ovaries	(g)	0.1438	0.1417	0.1256*	0.1004*
	(%)	0.041	0.042	0.037	0.035**
	(g/100 g brain)	7.38	7.19	6.48**	5.20**

*Statistical significance: *p<0.05; **p<.001*

10% reduction of ovary weight compared to control females (0.144 g) gives a value of 0.130 g. Interpolation between 5 and 25 mg/kg bw/day to a dose level which would be expected to result in ovary weights of 0.130 g gives a value of 21 mg/kg bw/day.

(Calculations: (25 – 5)/(0.142– 0.127) = 20/0.015 = 1333; 0.142 – 0.130 = 0.012; 0.012 x 1333 = 16; 5 + 16 = 21 mg/kg bw/day)

ED_{10} based on 10% reduction in seminal vesicles weight

Table 10. Data from the one-generation study (Knapp *et al.*, 2005)

Organ/tissue	Weight	Dose level (mg/kg bw/day)			
		0	5	25	125
Seminal vesicle	(g)	2.49	2.20**	2.10**	1.39**

*Statistical significance: *p<0.05; **p<.001*

A 10% reduction of the seminal vesicles weight compared to that of control males (2.49 g) gives a value of 2.24 g. Interpolation between 0 and 5 mg/kg bw/day to a dose level

which would be expected to result in seminal vesicles weight of 2.24 g gives a value of 4.3 mg/kg bw/day.

(Calculations: (5 – 0)/(2.49 – 2.20) = 5/0.29 = 17.2; 2.49 – 2.24 = 0.25; 0.25 x 17.2 = 4.3; 0 + 4.3 = 4.3 mg/kg bw/day)

Based on the above data and in line with the criteria given in table 3.7.2.5.4 of the Guidance on the Application of the CLP Criteria, preliminary assignment of TPP was to the medium potency group, because its lowest ED_{10} (4.3 mg/kg bw/day) in rats is within the limits of this potency group (4 – 400 mg/kg bw/day). The other ED_{10}-values calculated also fall within these limits.

Modifying factors

In the guidance (point 3.7.2.5.5 of the Guidance on the Application of CLP criteria), it is stated that other factors, so called modifying factors, should be taken into account to establish whether the preliminary calculated potency needs to be modified. These factors, and the conclusion on each of them with regards to the potency of TPP, are presented one-by-one below.

Type of effect/severity (point 3.7.2.5.5.1 of the Guidance on the Application of CLP criteria)

The effects of TPP on fertility and sexual function in rats are not considered to be of very high severity, something that could potentially move the substance into a higher potency group, because even at doses inducing marked parental toxicity or repeated dose toxicity the effect on fertility was moderate, and was expressed mostly as a reduction in the weight of ovaries or male accessory sex organs and mild alterations of the oestrous cycle. Hence, TPP need not be moved to another potency group based on this modifying factor.

Data availability (point 3.7.2.5.5.2 of the Guidance on the Application of CLP criteria)

The data on reproductive toxicity of TPP are based on one- and two-generations studies, a prenatal toxicity study and repeated dose toxicity studies relevant for assessment of effects on sex organs, therefore there is no need to modify the assessment of potency due to limited data availability.

Dose-response relationship (point 3.7.2.5.5.3 of the Guidance on the Application of CLP criteria)
The findings from studies used for assessment of reproductive toxicity show a clear dose-response relationship, with some effects observed only at the highest used dose, e.g., reduced fertility in the one-generation study. TPP, based on LOAELs and on ED_{10}, should be assigned to the medium potency group, since there were no effects observed below 5mg/kg bw/day in one- or two-generation studies, while in repeated dose toxicity studies the NOAEL/LOAEL were at the level of 100 mg/kg bw/day, thus higher than the lower limit of 4 mg/kg bw/day and lower than 400 mg/kg bw/day, which is the upper limit of the medium potency group.

Mode or mechanism of action (point 3.7.2.5.5.4 of the Guidance on the Application of CLP criteria)

The mechanistic studies indicate that TPP has weak estrogenic activity, and may have a weak anti-androgenic effect. However, the adverse effects of TPP on fertility and sexual function in rats, which might be mediated by these mechanisms, are seen at dose levels also inducing general toxicity with reduced body weight and feed consumption.
Therefore, in the opinion of RAC there is no need to move TPP to another potency groups based on its estrogenic or anti-androgenic activity.

Toxicokinetics (point 3.7.2.5.5.5 of the Guidance on the Application of CLP criteria)

There are no data which would allow comparison of TPP toxicokinetics between rats and humans; therefore it will not influence its assignment to the medium potency group.

Conclusion

Conclusion on classification

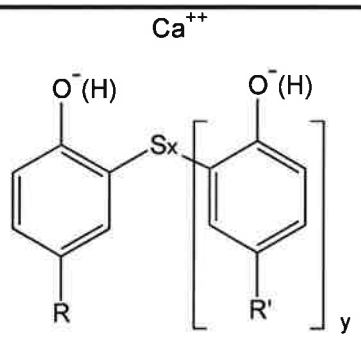
RAC concluded that TPP fulfils the criteria for classification as Repr. 1B, H360F according to the CLP Regulation and as Repr. Cat. 2; R60 according to the DSD. RAC further concluded that the existing data did not warrant classification of TPP as a developmental toxicant or classification for effects on or via lactation.

Conclusion on concentration limits

For medium potency substances the Guidance on the Application of the CLP criteria set 0.3% as the concentration limit (i.e. the general concentration limit according to the CLP criteria applies) for reproductive substances classified as Repr. 1B, and hence, based on that any preparation containing TPP at concentration equal to or in excess of 0.3% shall be classified with respect to reproductive toxicity, as Repr. 1B – H360F.

Annex 2 : SUMMARY CONCLUSIONS OF THE SIAR for Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category (from OECD SIDS SIAR for SIAM 28, 2009 by UK for Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category).

Category name	Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category
CAS Nos.	Sponsored Substances 68815-67-8 68855-45-8 122384-85-4 68784-25-8 122384-86-5 68784-26-9 122384-87-6 73758-62-0 122384-84-3 Supporting Substance 68515-93-5
Chemical Names	Sponsored Substances Phenol, thiobis[tetrapropylene-] Phenol, tetrapropenyl-, sulfurized, calcium salts Phenol, tetrapropenyl-, sulfurized, calcium salts, carbonates Phenol, tetrapropenyl-, sulfurized, carbonates, calcium salts, overbased Phenol, tetrapropenyl- and C18-30 alkyl derivatives, sulfurized, calcium salts, overbased

	Supporting Substance Phenol, nonyl derivatives, sulfides
Structural Formulae	 R, R' = median carbon chain length (see text) x = 1-3 bridging sulfur molecules y = 1-3 alkyl phen(ol)ate molecules Sponsored Substances C36H46O2S1-2 C36H58Ca2O4S1-3 C36H58Ca4O10S1-3 C42-54H70-94Ca4O10S1-3 Supporting Substance C30H46O2S1-2

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue rationale

The substances that make up the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide are complex mixtures that can vary in a number of generally predictable ways, and their structural similarities and predictability allow their assessment as a "continuum" category. The members of this category are mixtures of oligomers of alkyl phenol or alkyl phenate molecules that are linked by one to three sulfur atoms. The alkyl phenoxy group that is common to all the members of the category can contain saturated branched chain C10-C15 (predominantly tetrapropenyl) or saturated linear C18-C30 (alpha-olefin) alkyl groups (R and R') attached primarily at the para ring position. Alkyl phenate sulfides are made when the alkyl phenol group is reacted with calcium hydroxide or oxide to form the corresponding calcium salt. Alkyl phenol sulfides are not neutralized with calcium hydroxide during their manufacture.

The category members are produced using highly refined lubricant base oil as solvent. It must be emphasized that the CAS number assigned to each substance refers to the active alkyl phenol sulfide or calcium alkyl phenate sulfide ingredient,

but that these substances are never isolated from the highly refined lubricant base oil (present at 40 – 50%); isolation is not technically possible without incurring degradation of the phenate sulfide. Consequently, the measured data presented represent the results of tests conducted with the test substance as manufactured, and the purity of the test substances and amount of highly refined lubricant base oil varies based on the manufacturing processes used by the different manufacturers of these substances. However, calculated data (e.g. QSAR estimates) represent the results of the theoretically purified substance without highly refined lubricant base oil. In general, highly refined lubricant base oils used in the manufacture of alkyl phenol sulfides and alkyl phenate sulfides may cause slight skin irritation, but otherwise have a low order of acute and chronic toxicity. However, the presence of highly refined lubricant base oil can have an impact on the results of aquatic toxicity tests and environmental fate tests where the alkyl phenol sulphide or alkyl phenate sulphide would tend to remain in the lubricant base oil fraction of the mixture and enter the water column to a limited degree in accordance with the log Kow of the substance.

The substances in this category contain the unreacted alkyl phenol and its calcium salts in varying amounts as an unintended residual resulting from the processes involved in manufacture. One example is unreacted tetrapropenyl phenol (TPP, CAS # 74499-35-7) previously assessed in the OECD HPV programme) and its calcium salt (CaTPP), which has been shown to be present in representative samples of the tetrapropenyl phenate sulfide and carbonates (at 3 – 14%). TPP has low solubility in water, high log Kow, and low vapour pressure. It is highly toxic to aquatic organisms, and it causes adverse systemic effects in repeated-dose toxicity studies in mammals. It also causes adverse effects on reproduction parameters and reproductive organs and adverse effects on the developing fetus in mammals. These effects are discussed further below.

The physico-chemical data indicate that the category members demonstrate an orderly progression of changes as one goes from lower molecular weight to higher molecular weight in the category. The physico-chemical information provided indicates that boiling point and log Kow increases across the category, and vapour pressure and water solubility decrease across the category. These physico-chemical properties indicate that the group members are likely to have limited mammalian bioavailability. This is supported by the findings from the single and repeated exposure mammalian toxicity studies indicating minimal general toxicity. All category members have a low vapour pressure indicating that inhalation of vapours is not a likely route of exposure for humans or in the environment. Based on the physico-chemical properties of low water solubility and high octanol-water partition coefficient, these substances are likely to partition largely to sediment and suspended solids in the aquatic environment.

A saturated branched C9 (nonyl) chain substance (CAS 68515-93-5) is used as a supporting substance. This substance is closely related to the category members, differing only in the length of the alkyl chain. Measured data from this supporting substance are used for water solubility and acute inhalation toxicity endpoints.

Physico-chemical properties

The substances that are members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide Category are complex reaction mixtures. As stated above, the measured data presented represent the results of tests conducted with the test substance as manufactured, which contains up to 50% highly refined mineral oil that cannot be removed. Calculated data represent the results of the theoretically purified substance without highly refined lubricant base oil, based on the neutral phenol compounds. Therefore calculated values should be viewed as indicative rather than prescriptive. They are liquids with low water solubility (less than 0.206 mg/L, measured, for the supporting substance nonyl phenol sulfide – CAS No.

68515-93-5) and low vapour pressure (calculated range 3 x 10-12 – 6.2 x 10-29 Pa at 25°C). The octanol-water partition coefficient for these substances is high (log Kow > 6.6, measured). Calculated log Kow values range between 8.5 and 14.

Human health

It is known that these materials have varying levels of residual TPP present and that this substance has demonstrated the potential for toxicity to human health in its own right. This information should therefore be borne in mind as the dataset for this group of materials is considered as it is likely to have some impact for certain endpoints. At this time, however, it is not possible to say with any certainty for which endpoints TPP is a major contributing factor as the evidence is not sufficient to warrant such a statement. It can be stated with some confidence that it is likely to play at least some role in several of the endpoints (e.g. reproductive toxicity) and so considerations to this effect have been included within these sections as a potential explanation for some of the results. Without further testing it would be unwise to speculate on the association between this substance and other endpoints for human health. A summary of the toxicity of TPP is provided in the Appendix to the main SIAR document for reference and comparison.

No experimental data on toxicokinetics of category members are available. The high lipophilicity, high molecular weight, low aqueous solubility, and the lack of adverse findings following oral and dermal dosing indicate that intestinal absorption or absorption through the skin and distribution in the body is likely to be limited. The low vapor pressures of these substances indicate that very little if any absorption occurs via inhalation. Metabolism to (non-toxic) metabolites is predicted to occur mostly in the liver. Excretion is expected to be mainly via the urine and feces.

In general, members of the category are not acutely toxic. In the key acute oral toxicity study (OECD TG 401) for each category member, the LD_{50} ranged from >5000 to >16000 mg/kg. No deaths occurred in these studies, and signs of toxicity included dirty ruffled fur, soft feces, dark-stained urogenital areas, and red-stained feces at dose levels >5000 mg/kg. The LD_{50} in the key acute dermal toxicity studies (OECD TG 402) available for all the category members (except CAS # 68815-67-8) plus the supporting substance (CAS # 68515-93-5) ranged from 2000 to 5000 mg/kg, No deaths occurred in these studies, and signs of toxicity included a decrease in food consumption and clear ocular discharge at dose levels >4000 mg/kg. In two acute inhalation studies (similar to OECD 403) in rodents with CAS # 122384-87-6 and supporting substance CAS # 68515-93-5, no signs of toxicity occurred at concentrations of up to 1.67 mg/L

In the key eye irritation studies (OECD TG 405) for each category member, animal data indicate that these substances cause slight reversible conjunctival irritation: corneal opacity was observed in only one animal in one study (with CAS # 122384-85-4) and cleared by 24 hours.

Slight reversible irritation to the skin was observed in the key skin irritation studies (OECD TG 404) for each member of the category following a 4-hour application to the skin. In general, skin irritation scores were slightly higher in studies where the test substance was applied to the skin for 24 hours in older studies. In two repeated-dose dermal toxicity studies in rats (CAS # 122384-87-6) and rabbits (supporting substance CAS # 68515-93-5), application of the test substances over a 28-day period resulted in skin irritation at the application site). However, in 2 human repeated-insult patch tests in which the same test substances were applied three times per week for three weeks, no evidence of skin irritation was observed.

Several skin sensitization studies (OECD TG 406) in guinea pigs have been conducted for each member of the category. Findings in animal studies present a contradictory profile, with positive and negative results in some instances

obtained with the same substance following identical protocols. However, negative findings were obtained in two human repeated-insult patch tests with CAS # 122384-87-6 and supporting substance CAS # 68515-93-5. Overall, these substances are not considered to be sensitisers in humans.

The repeated-dose toxicity of the members of this category has been evaluated in two 28-day repeated-dose oral (gavage) toxicity studies (OECD TG 422), one repeated-dose dermal toxicity studies (OECD TG 410), two oral (gavage) developmental toxicity studies (based on OECD TG 414), and a 2-generation oral (gavage) reproductive toxicity study (OECD TG 416).

The 28-day repeated-dose oral (gavage) toxicity study with CAS # 122384-85-4 was conducted in rats with dose levels of 0, 50, 300, and 1000 mg/kg bw/day for 7 days/week for 4 weeks. The sample of the test substance used in this study was a commercial sample that contained 54% alkyl phenate sulphide oligomers, 43% highly refined lubricant base oil, and 3% unreacted tetrapropenyl phenol (TPP) and the calcium salt of TPP (CaTPP). Consequently, the animals in the high-dose group were administered 30 mg/kg bw/day of TPP and CaTPP. No deaths occurred, and no signs of toxicity were observed in this study. At study termination, increased mean adrenal weights (absolute and relative to brain weights) were observed at the high dose of 1000 mg/kg bw/day in females only. These changes were accompanied by an increase in the severity of fine vacuolar changes in the cells of the zona fasciculate in the adrenal cortex in the high-dose females. The NOAEL for this study was 300 mg/kg bw/day. Although TPP caused an increase in mean adrenal weights in a 28-day repeated-dose oral (gavage) toxicity study and a 1-generation oral (gavage) reproductive toxicity study, those changes occurred at dose levels >180 mg/kg bw/day in the 28-day study and at the high dose of 125 mg/kg bw/day in the reproductive toxicity study, these changes occurred only in males and was accompanied by a decrease in mean body weight gain. The TPP concentration in the high-dose group in this study was well below the dose levels of TPP that caused adverse effects on the adrenal gland. Hence these findings do not support a possible relationship between the toxicity of TPP and the adverse effects on the adrenal glands observed in this study.

The 28-day repeated-dose oral (gavage) toxicity study with CAS # 122384-87-6 was conducted in rats with dose levels of 0, 50, 200 and 1000 mg/kg bw/day also for 7 days/week for 4 weeks. The sample of the test substance used in this study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. Consequently, the animals in the high-dose group were administered 67 mg/kg bw/day of TPP and CaTPP. No deaths occurred in this study. Signs of toxicity observed one hour after dosing were limited to salivation, clear material around the mouth, red or yellow staining around the mouth and/or red material around the nose in males and females receiving 1000 mg/kg bw/day. Mean body weight gain was decreased in males and mean adrenal weights (absolute and relative to brain weights) were increased in males and only slightly in females. There were no microscopic changes in any tissues attributable to treatment, and the NOAEL for this study was 200 mg/kg bw/day. The decrease in mean body weight gain and the increase in mean adrenal weight in this study are qualitatively similar to those findings in the repeated-dose studies with TPP. Hence these findings would tend to support a possible relationship between the toxicity of TPP and the adverse effects on the adrenal glands observed in this study.

The 28-day repeated-dose dermal toxicity study with CAS # 122384-87-6 in rats was conducted with dose levels of approximately 0, 20, 100 and 250 mg/kg bw/day administered for six hours/day, 5 days/week for 4 weeks. The concentration of TPP was not measured in the test sample. No deaths or systemic

toxicity was observed in this study, and the systemic NOAEL was 250 mg/kg bw/day.

In the two oral (gavage) developmental toxicity studies in rats, CAS # 122384-87-6 was dosed at levels of 0, 50, 300, 1000 mg/kg bw/day from Days 6-16 of gestation. The TPP concentration was not measured in the sample of commercial test substance used in the screening study. The sample of the test substance used in the definitive study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. The test substance was administered to 14 or 15 inseminated females at each dose level in the screening study and to 25 inseminated females at each dose level in the definitive study. No deaths or signs of toxicity attributable to the test substance were observed in the screening study, and treatment-related signs of toxicity observed in the definitive study were limited to clear, red, yellow and/or tan staining/matting/material around the nose and mouth in the high-dose group. In both studies, there was a decrease in mean maternal body weight gain on Days 6-16. The NOAEL for systemic toxicity in both studies was 300 mg/kg bw/day.

The 2-generation oral (gave) reproductive toxicity study in rats with CAS # 122384-87-6 was conducted using dose levels of 0, 50, 200 and 1000 mg/kg bw/day for 7 days/week for 10 weeks prior to mating and all through mating, gestation and lactation for two generations. The sample of the test substance used in this study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. There were no deaths in this study that could be attributed to the test substance. The predominant signs of toxicity included yellow, red, brown, tan, and/or clear staining/matting/material on various body surfaces, salivation, and red discharge from the vaginal opening at the high dose of 1000 mg/kg bw/day. A decrease in mean body weights in F0 and F1 males in the high-dose group and F1 (but not F0) males in the mid-dose group were observed. There were no effects on mean body weights in females at any dose at any time in the study, except at gestation in the high-dose group. Mean pituitary weights (absolute and relative to final body weight) were increased at the high-dose level in both F0 and F1 males and females and at the mid-dose level in the F0 males only. Mean liver weights (absolute and relative to final body weight) were also increased in the F0 and F1 females at the high dose level. No microscopic lesion attributable to the test substance was observed in these or any other tissue in either sex. The NOAEL for systemic toxicity in this study was 50 mg/kg bw/day.

All of the members of this category are not mutagenic in vitro based on the results of bacterial reverse mutation tests (OECD TG 471) for each member of the category and two mutation assays in cultured mammalian cells (OECD TG 476) with CAS # 68815-67-8 and CAS # 122384-87-6. No positive evidence of in vivo genotoxicity was found in a mouse micronucleus assay (OECD TG 474) conducted with CAS # 122384-85-4 at dose levels up to 5000 mg/kg via intraperitoneal injection.

There is no information on the carcinogenic potential of the any of the category members.

Two members of the category (CAS # 122384-85-4 and CAS # 122384-87-6) were evaluated for reproductive toxicity in oral (gavage) reproductive toxicity screening studies (OECD TG 422) in rats. A 2-generation oral (gavage) toxicity study (OECD TG 416) in rats was conducted with CAS # 122384-87-6 after adverse effects were noted in the reproductive toxicity screening test with this test substance.

In the oral (gavage) reproductive toxicity screening study with CAS # 122384-85-4, the test substance was administered to male and female rats at dose levels

of 0, 50, 300 and 1000 mg/kg bw/day for 7 days/week for four weeks prior to mating. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dsoe group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. There were no adverse effects on any reproductive parameter in this study. The NOAEL for reproductive toxicity is 1000 mg/kg bw/day. The amount of TPP administered in the high dose in this study, 30 mg/kg bw/day, is well below the dose of TPP that caused reproductive toxicity in the 1-generation study.

The oral (gavage) reproductive toxicity screening study with CAS # 122384-87-6 was conducted with dose levels of 0, 50, 200 and 1000 mg/kg bw/day administered to males and females for 7 days/week for 4 weeks prior to mating. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dose group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. The systemic toxicity observed in this study has been described in the repeated-dose toxicity section above. The test substance caused a decrease in mean live litter size and a decrease in the mean number of corpora lutea for each female at the high dose of 1000 mg/kg bw/day. No other significant effects on reproduction parameters or reproductive organs were observed in this study. The NOAEL for reproductive toxicity was 200 mg/kg bw/day.

In the 2-generation oral (gavage) reproductive toxicity test with CAS # 122384-87-6, the test substance was administered to male and female rats at dose levels of 0, 50, 200 and 1000 mg/kg bw/day for 7 days/week for 10 weeks prior to mating and all through mating, gestation and lactation for two generations. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dose group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. The F0 and F1 fertility indeces (number of pregnant females/number of mated females) and F0 and F1 mean live litter sizes were significantly reduced at the high dose of 1000 mg/kg bw/day. In addition, F0 and F1 mean testes, epididymides, and ovary weights were decreased and F0 and F1 mean pituitary weights were increased in males and females. Qualitative spermatogenesis evaluations were performed on all males that did not sire a litter, but no treatment-related changes were observed in gross sperm morphology, apparent relative numbers or motility in the epididymides. The reproductive NOAEL for this study is 200 mg/kg bw/day.

Although the amount of TPP administered in the high dose group in both reproductive toxicity studies with CAS # 122384-87-6, 67 mg/kg bw/day, is lower than the lowest dose of TPP that caused adverse effects on reproduction parameters and reproductive organs in the one-generation reproductive toxicity study, it is also higher than the dose level that did not cause reproductive toxicity. Consequently, the adverse results on reproduction with CAS # 122384-87-6 are consistent with the adverse effects on reproduction produced by TPP.

In two oral (gavage) developmental toxicity studies in rats, CAS # 122384-87-6 was dosed at levels of 0, 50, 300, 1000 mg/kg bw/day from Days 6-16 of gestation. The TPP concentration was not measured in the sample of commercial test substance used in the screening study. The sample of the test substance used in the definitive study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. The test substance was administered to 14 or 15 inseminated females at each dose level in the screening study and to 25 inseminated females at each dose level in the definitive study. No deaths or signs of toxicity attributable to the test substance were observed in the screening study, and treatment-related signs of toxicity observed in the definitive study were limited to clear, red, yellow and/or tan staining/matting/material around the nose

and mouth in the high-dose group. In both studies, there was a decrease in mean maternal body weight gain on Days 6-16. In the screening study, a significant increase in the incidence of fetuses and litters with 14th rudimentary ribs was observed at the high dose of 1000 mg/kg/day. In addition, there was an increased incidence of fetuses with non-ossified and/or incomplete ossification of the hyoid at the mid- and high-dose levels. However, there was no increased incidence of litters with this skeletal variant at any dose level. In the definitive study, there was an increased incidence of litters with bent ribs in the high dose of 1000 mg/kg bw/day. However, the incidence of fetuses with this skeletal variant was not increased. The findings on the ribs in both studies are regarded as minor variations and not major malformations. The delayed ossification of the hyoid may well represent an increase in a finding with a high spontaneous background incidence. The NOAEL for developmental toxicity in the screening study is 50 mg/kg bw/day, and the NOAEL for developmental toxicity in the definitive study is 300 mg/kg bw/day. Overall, minor developmental variations were noted in rats.

In summary, the members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category, are of a low order of toxicity after acute oral and dermal exposure. These substances cause slight irritation to the eye and skin, and they are not human skin sensitizers. Repeated-dose toxicity studies show some evidence of systemic toxicity at the limit dose of 1000 mg/kg bw/day and at 200 mg/kg bw/day in a 2-generation study. The members of this category are not mutagenic *in vitro*. They are of low concern for developmental toxicity. Alkyl phenate sulfides cause a reduction in fertility in males and female rats, a reduction in mean live litter size, and a reduction in the size of male and female reproductive organs. This may be dependent on the concentration of residual unreacted TPP + CaTPP. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

It can be concluded that the substances that are members of the category do not readily biodegrade. In two studies conducted with CAS # 122384-85-4, the extent of biodegradation after 28 days ranged from 4.7% to 13.4% (OECD TG 301B). They do not undergo hydrolysis. Atmospheric half-lives ranging from 1. 41 to 3.00 hours can be calculated based on hydroxyl radical interaction, but the low vapour pressure of these substances and their Henry's Law Constants indicate that partitioning into atmosphere will not be a significant pathway. The Equilibrium Criterion (EQC) model, part of the EPISUITE program, indicates that these substances are likely to preferentially bind to soil in the terrestrial environment and to sediment and suspended particles in the aquatic environment. While the octanol-water partition coefficient for these substances is high (log Kow > 6.6, measured), calculated bioconcentration factors based on calculated log Kow values (range 8.5 - 14) generally suggest that these substances have low bioaccumulation potential (estimated BCF range 3.2 – 656). This is supported by an in vitro membrane transport study and the substances' properties indicating low bioavailability in aqueous media.

The substances that make up this category are of low concern for acute toxicity to aquatic organisms. Due to the physico-chemical properties of the substances in this category, water accommodated fractions (WAF) were generally used to produce test media in aquatic studies. Results are quoted relative to WAF loading rates. The WAFs, prepared from loading rates of at least 100mg/l, did not exert acute toxic effects on fish, invertebrates, or algae.

CAS 122384-85-4:

OECD TG 203, *Pimephales promelas* 96h LL50 > 1000mg/l (WAF)

OECD TG 203, *Oncorhynchus mykiss* 96h LL50 > 1000mg/l (WAF)

OECD TG 202, *Daphnia magna* 48h LL50 > 1000mg/l (WAF)

OECD TG 201, *Pseudokirchneriella subcapitata* 96h LL50 > 1000mg/l (WAF)

CAS 122384-86-5:

OECD TG 203, *Pimephales promelas* 96h LL50 (growth rate) > 1000mg/l (WAF)

OECD TG 202, *Daphnia magna* 48h LL50 > 1000mg/l (WAF)

OECD TG 201, *Pseudokirchneriella subcapitata* 96h LL50 > 500mg/l (WAF)

CAS 122384-84-3:

OECD TG 203, *Oncorhynchus mykiss* 96h LL50 > 10,000mg/l (WAF)

These substances are not expected to inhibit wastewater treatment plant microorganisms at typical discharge rates (the 3-hr EC50 is greater than 1,000 mg/L (nominal) in activated sludge respiration inhibition tests). No data on chronic toxicity are available.

The data for this group of materials in this section are not easy to interpret for a number of reasons. These include the unavoidable presence of base oil in the mixtures (which may impact the soluble fractions of the category members and have its own effects on organisms), WAF testing (and variations in WAF methods), and lack of analytical methods to measure the levels and composition of the dissolved fraction for such insoluble materials (making determination of actual exposures tested not possible). A further complication is the presence at varying levels of residual TPP (tetrapropenylphenol, branched C12 alkylphenol) which is known to have a number of effects on test organisms. In WAF preparation it is likely that those components present with higher water solubilities will preferentially dissolve, so that the proportions of the components in the test water are not representative of the proportions of the components found in the test material itself. Relative concentrations will be skewed in favour of the more soluble components. The lower molecular weight/shorter alkyl chain constituents, such as TPP, appear to be more water soluble than the larger components. All of these factors, particularly the TPP presence, make the interpretation of toxicity tests with these substances complex. No acute effects were observed in the valid studies conducted using a WAF technique. There is no data for long term exposure; but it is plausible that the more soluble components (that may be over-represented in the WAF test media, such as TPP) may exhibit effects in long term studies. A summary of TPP toxicity is provided in the Appendix to the main SIAR document for reference and comparison. In the environment the substances are likely to partition to sediment in the aquatic compartment and bind to soil in the terrestrial environment; no data for sediment- or soil-dwelling organisms are available.

In summary, while there are a number of potentially confounding variables within the data, the substances in this category do not appear to present an acute aquatic toxicity hazard for the environment. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

The substances that are members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide Category are produced in closed processes in France, the United

Kingdom, Singapore, and United States of America. The total global production volume is estimated to be greater than 43,000 tonnes/year.

Members of this category are used to formulate finished lubricant oils including all types of automotive and diesel engine crankcase oils, marine and railroad diesel engine oils, and air-cooled two-cycle engine oils. Typical finished oils contain 1 to 10% alkyl phenol sulfide or alkyl phenate sulfide.

Occupation and consumer exposure to the category members is in general expected to be very low based on their physico-chemical properties, use and handling patterns. Some dermal exposure is expected due to the widespread use of these substances in all types of engine oils. Potential releases of the category members to the environment may occur following production, use to make lubricant additive packages, blending lubricant additives into finished oils, and use and disposal of used lubricants.