Danish Ministry of the Environment
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION and EVALUATION REPORT

for

Oligomerisation and alkylation reaction products of 2-phenylpropene and phenol (OAPP)

List No 700-960-7

Evaluating Member State Competent Authority: Denmark

Dated: 24 April 2024

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Further information on registered substances here:

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

Further information on the substance evaluation process here:

https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation

Foreword

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the outcome of the Substance Evaluation carried out by the evaluating MSCA. The document consists of two parts i.e. A) the conclusion and B) the evaluation report.

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 MSCA. In case the evaluating MSCA 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 MSCA, it does not preclude other MSCAs or the European Commission from initiating regulatory risk management measures which they deem appropriate.

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Part A. Conclusion

In the conclusion (part A), the evaluating MSCA 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.

Alternatively, the outcome of the evaluation may be that presently there is no need for regulatory follow-up at EU level if sufficient information on the potential hazards is available and all necessary measures for safe handling of the substance are in place.

1. Scope of the evaluation

Oligomerisation and alkylation reaction products of 2-phenylpropene and phenol (OAPP, the Substance) was originally selected for substance evaluation to clarify the following concerns:

PBT/vPvB
Endocrine disruption (environment)
Endocrine disruption (human health)
Wide dispersive use
High (aggregated) tonnages

During the evaluation, no additional concerns were identified.

2. Overview of other processes / EU legislation

Table 2.-1 Overview of other processes / EU legislation

No other processes	CCH	TPE	GMT	Previously on CoRAP	Annex VI (CLP)	Annex XVII (Restriction)	Candidate List/Annex XIV (Authorisation)
☐	☒	☒	☐	☐	☐	☐	☒

Other EU legislation PPP/BPR	Previous legislation NONS/RAR	Stockholm convention POP	Other (e.g., UNEP)
☐	☐	☐	☐

3. Conclusion and regulatory follow-up action

The evaluation of the available information on the Substance has led the evaluating MSCA to the following conclusions.

Table 3.-1 Conclusion and regulatory follow-up action

Initial and additional concern	Conclusion on concern	Regulatory follow-up action
PBT/vPvB	Concern confirmed. A trimer constituent in OAPP, 1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan, fulfils vPvB criteria.	Identification as SVHC (authorisation)
Endocrine disruption (human health)	Concern removed (clarification of hazard/exposure)	No need for regulatory follow-up at EU level
Endocrine disruption (environment)	Concern confirmed for 4-(*α,α*-dimethylbenzyl)phenol constituent in OAPP.	Regulatory follow-up at EU level to be considered

4. Regulatory follow-up actions at EU level

4.1 Harmonised Classification and Labelling

Styrenated phenol (EC 262-975-0, CAS RN 61788-44-1) has been assessed by the German MSCA identifying a need for follow-up regulatory action at EU level. Joint actions on the ED environment endpoint for the Bisphenol A (BPA) analogue present as a constituent in the UVCBs could be considered in the future. Whether to go via an SVHC or CLH route is yet to be decided.

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

OAPP has been identified as a substance of very high concern (SVHC) as it contains a constituent which fulfils the criteria for vPvB.

4.3 Restriction

Not applicable

4.4 Other EU-wide regulatory risk management measures

Not applicable

5. Currently no need for regulatory follow-up at EU level

Not applicable

6. Tentative plan for follow-up actions

As indicated in Table 3.-1, the following regulatory action(s) at EU level are proposed.

Regulatory actions on the ED environment endpoint for the BPA analogue in the UVCBs could be considered in the future. Whether to go via an SVHC or CLH route is yet to be decided.

Indication of a tentative plan is not a formal commitment by the evaluating MSCA. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 6.-1 Follow-up actions

Follow-up action	Date for intention	Actor
Either SVHC Identification (authorisation)	tbd	tbd
Or Harmonised C&L	tbd	tbd

Part B. Substance evaluation report

In the substance evaluation report (part B), the document provides explanation how the evaluating MSCA assessed and drew the conclusions from the information available.

7. Overview of the Substance Evaluation Process

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA evaluated the Substance based on the information in the registration dossier(s) and on other relevant and available information.

Before concluding the substance evaluation, a Decision to request further information was issued according to Article 46 on 24 February 2014.

In this decision, two studies were requested to further clarify the PBT and ED concern related to OAPP, which now have been conducted and evaluated:

- A combined repeated dose 90-day toxicity study (OECD TG 408) and Extended one-generation reproductive toxicity study in rats, oral route (OECD TG 443) including the two cohorts for developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT)
- A combined OECD TG 305/229, bioaccumulation test in fish with vitellogenin (VTG) measurements (dietary exposure)

A follow-up decision, dated 15 December 2020, requested the registrant to:

- conduct an Aerobic mineralisation in surface water – simulation biodegradation test (OECD TG 309) on the constituent 1,1,3-trimethyl-3-phenylindan (CAS RN 3910-35-8)
- identify and clarify the composition and structure of C9 trimers present in the Substance.

With regards to the initial concern for PBT/vPvB, the dimer fraction fulfils the 'B'-criterion and the trimers fulfil the 'vB'-criterion based on the combined OECD TG 305/229 study. The phenolic fraction is assessed to not be 'B' or 'vB' and, for these constituents, the PBT concern is considered to be removed.

Simulation testing in surface water on the dimer 1,1,3-trimethyl-3-phenylindan (EC 223-467-4, CAS RN 3910-35-8) shows that the dimer fulfils the P/vP criteria of REACH Annex XIII. No experimental data is available for the trimers. Therefore, a read-across approach was used based on the structural similarity between the dimer 1,1,3-trimethyl-3-phenylindan (EC 223-467-4, CAS RN 3910-35-8) and the trimer 1,3-dimethyl-1-(2-methyl-2- phenyl)propyl-3-phenylindan (EC 255-584-1, CAS RN 41906-71-2) supported with (quantitative) structure-activity relationship ((Q)SAR) results in a weight-of-evidence approach. Based on a read-across approach with the dimer, it can be reasonably assumed that the trimer is at least as persistent as the dimer and thus the degradation half-life in water of the trimer exceeds 60 days. As a consequence, it is concluded that the trimer 1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan (EC 255-584-1, CAS RN 41906-71-2) is very persistent in water (degradation half-life >60 days) in accordance with REACH Annex XIII. On this basis, the Substance was identified as very persistent and very bioaccumulative (vPvB) according to Article 57 (e) of Regulation (EC) No 1907/2006 (REACH) on 29 November 2023.

In the combined OECD TG 443/408 study, the chosen top dose (1500 ppm corresponding to ~124 mg/kg bw/day) caused significant and consistent reductions in parental and offspring body weights in both sexes. The overall evaluation of all available information is that no indications of anti-androgenic or estrogenic effects of OAPP were observed in rats. Also, no signs of repeated dose, reproductive or developmental toxicity were observed in

the requested study. Based on this study, the initial concern for endocrine disruption for human health is considered clarified and no further action is needed.

On the initial concern for endocrine disruption for the environment, VTG induction was observed in the requested combined OECD TG 305/229 bioaccumulation test in fish. To address the environmental ED concern, the registrant also uses a positive Fish sexual development test (FSDT, OECD TG 234) conducted on 4-monostyrenated phenol (4-MSP, source) as part of a read-across to 4-(α,α-dimethylbenzyl)phenol (target). On this basis, the evaluating MSCA concludes that the available data indicate that the 4-(α,α-dimethylbenzyl)phenol constituent of the Substance acts as an endocrine disruptor for the environment and therefore, the Substance can be considered as an endocrine disruptor.

8. Substance identity

The information on the Substance including identifiers and structural formula can be found on the cover page. For more details, see ECHA: https://chem.echa.europa.eu

Oligomerisation and alkylation reaction products of 2-phenylpropene and phenol (OAPP) is a UVCB (substance of Unknown or Variable composition, Complex reaction products or of Biological Materials) and can therefore not be described by unique structures and molecular formulas. It consists of a number of constituents. Some of these constituents are the result of the alkylation of phenols where the phenol can be monoalkylated, dialkylated and trialkylated. Others are the result of the oligomerisation of 2-phenylpropene and include dimers and trimers of relatively similar structures.

The registered substance has been previously identified with the name phenol, methylstyrenated and EC 270-966-8 and CAS RN 68512-30-1**.**

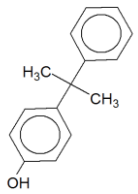
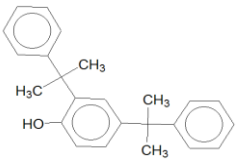
Synonyms: OAPP; phenol, methylstyrenated

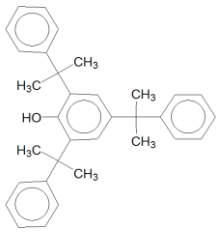
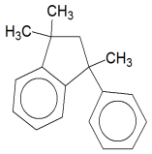
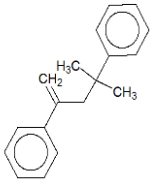
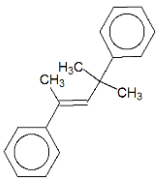
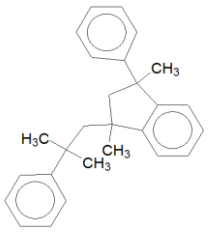
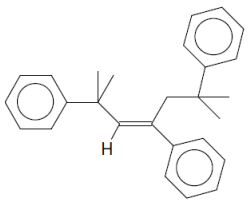
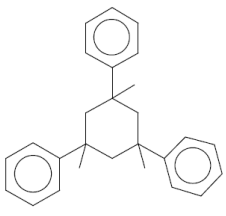
8.1. Type of Substance

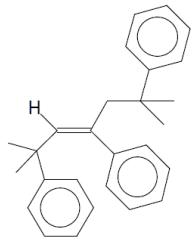
UVCB

8.2. Other relevant information

Table 8.2.-1 Constituents

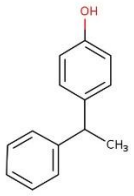
Constituents	Structure
4-(*α,α*-dimethylbenzyl)phenol EC no.: 209-968-0 CAS RN: 599-64-4 Type: monoalkylated phenol	
2,4-bis(1-methyl-1-phenylethyl)phenol EC no.: 220-466-0 CAS RN: 2772-45-4 Type: dialkylated phenol	

Constituents	Structure
2,4,6-tris(1-methyl-1-phenylethyl)phenol EC no. : 250-325-9 CAS RN: 30748-85-7 Type: trialkylated phenol	
1,1,3-trimethyl-3-phenylindan EC no.: 223-467-4 CAS RN: 3910-35-8 Type: dimer	
1,1’-(1,1-dimethyl-3-methylene-1,3- propanediyl)bisbenzene EC no.: 228-846-8 CAS RN: 6362-80-7 Type: dimer	
1,1’-(1,3,3-trimethylprop-1-ene-1,3-diyl)dibenzene EC no.: 228-396-2 CAS RN: 6258-73-7 Type: dimer	
1,3-dimethyl-1-(2-methyl-2-phenylpropyl)-3-phenylindan EC no.: 255-584-1 CAS RN: 41906-71-2 Type: trimer	
1,1',1''-[(3*E*)-2,6-dimethylhept-3-ene-2,4,6-triyl]tribenzene Type: trimer	
1,3,5-triphenyl-1,3,5-trimethylcyclohexane Type: trimer	

Constituents	Structure
1,1',1''-[(3*Z*)-2,6-dimethylhept-3-ene-2,4,6-triyl]tribenzene CAS RN: 957070-06-3 Type: trimer	

8.3. Analogue substance (read-across)

Table 8.3.-2 Relevant analogue substance

EC/List number	CAS RN	Public Substance name	Chemical structure
217-864-1	1988-89-2	p-(1-phenylethyl)phenol	

9. Physicochemical properties

Table 9.-1 Overview of physicochemical properties

Property	Value
Molecular weight/weight range	212-449
Physical state at 20°C and 101.3 kPa	At 20 °C and 1013 hPa, the substance is a colourless viscous liquid with a slightly phenolic odour.
Vapour pressure	The vapour pressure is between 0.03 and 0.06 Pa at 20 °C and between 0.05 and 0.09 at 25 °C. Vapour pressure at 100 °C was 22 Pa and 3030 Pa at 200 °C.
Water solubility	Due to the nature of the product, there is a range of water solubilities. The range begins at 0.5 mg total organic carbon (TOC)/L and extends to 7 mg TOC/L between 20 and 25 °C, depending on the nominal loading rate used. At a nominal loading of 100 mg/L, the water-accommodated fractions (WAF) amounted to 1.5 to 4 mg C/L, i.e. 1.5 to 4 %.
Partition coefficient n-octanol/water (Log K_{ow})	Due to the nature of the product, there is a range of log Kow values. The range begins at 3.6 and extends to beyond 6.3 at 25 °C.

10. Manufacture and uses

10.1. Quantities

The aggregated tonnage (per year) of the Substance is 1,000 - 10,000 tonnes.

10.2. Overview of uses

Table 10.2.-1 Overview of uses

Main uses	Key information
Formulation or repacking	This substance is used in the following products: polymers, adhesives and sealants, coating products, fillers, putties, plasters, modelling clay and inks and toners. Release to the environment of this substance can occur from industrial use: formulation of mixtures and formulation in materials
Uses at industrial sites	This substance is used in the following products: adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, inks and toners and polymers. This substance is used in the following areas: building & construction work and printing and recorded media reproduction. This substance is used for the manufacture of: machinery and vehicles, wood and wood products, pulp, paper and paper products, electrical, electronic and optical equipment, furniture, rubber products and mineral products (e.g. plasters, cement). Release to the environment of this substance can occur from industrial use: in the production of articles, as processing aid, industrial abrasion processing with low release rate (e.g. cutting of textile, cutting, machining or grinding of metal) and industrial abrasion processing with high release rate (e.g. sanding operations or paint stripping by shot-blasting)
Uses by professional workers	This substance is used in the following products: adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, inks and toners and polymers. This substance is used in the following areas: building & construction work. This substance is used for the manufacture of: wood and wood products, machinery and vehicles, furniture, electrical, electronic and optical equipment and plastic products. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use
Consumer uses	This substance is used in the following products: adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, inks and toners and polymers. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners), outdoor use, outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment)
Article service life	Release to the environment of this substance can occur from industrial use: in the production of articles. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners), outdoor use, outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment). This substance can be found in complex articles, with no release intended: vehicles and machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines). This substance can be found in products with material based on: stone, plaster, cement, glass or ceramic (e.g. dishes, pots/pans, food storage containers, construction and isolation material), wood (e.g. floors, furniture, toys), paper (e.g. tissues, feminine hygiene products, nappies, books, magazines, wallpaper) and rubber (e.g. tyres, shoes, toys)

11. Classification and labelling

Table 11.-1 Classification of the Substance

Harmonised classification (Annex VI of CLP)	Self-classification in registrations	Self-classification in C&L notifications
-	Skin Irrit. 2, H315 Skin Sens. 1B, H317 Aquatic Chronic 3, H412	-

12. Environmental fate properties

The substance is identified as vPvB based on the properties of the trimer constituent 1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan (EC 255-584-1, CAS RN 41906-71-2).

12.1. Degradation

12.1.1 Abiotic degradation

The available data for hydrolysis and oxidation, and AOPWIN v1.92 (US EPA, 2023) estimations for phototransformation in air are detailed in Section 3.1.1 of the available SVHC support document[1]. Based on the available data, the evaluating MSCA concludes that:

- hydrolysis under environmental conditions is unlikely as OAPP is composed of constituents that do not contain functional groups susceptible to hydrolysis;
- oxidation of the dimers and trimers is unlikely;
- the dimers are expected to undergo relatively rapid primary photodegradation in air based on their structure. The trimers are more resistant to photodegradation and may to a large extent not be photodegraded mainly due to sorption to airborne particulates. The distribution to air of the dimers and trimers is predicted to be very low. Hence, unless release of the substance is directly to air, this degradation pathway appears to be of minor importance.

12.1.2 Biodegradation

The current available biodegradation data and the evaluation by the evaluating MSCA is detailed in Section 3.1.2 of the SVHC support document[1] and briefly summarized below.

Estimated data for the dimers and trimers present in the Substance indicates that all trimer constituents screen as 'potentially P/vP' and the dimer constituents, while also 'potentially P/vP' require more degradation relevant information. OECD TG 301 ready biodegradability testing of the Substance reports that it is not readily biodegradable. Ready biodegradability testing of the constituents 4-(α,α-dimethylbenzyl)phenol (EC 209-968-0, CAS RN 599-64-4) and 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene (EC 228-846-8; CAS RN 6362-80-7) using testing equivalent to OECD TG 301 reported that the constituents are not readily biodegradable.

[1] https://www.echa.europa.eu/documents/10162/6c4b3401-858d-0b65-e5b1-1484fce3c84c

Simulation testing in surface water on the dimer 1,1,3-trimethyl-3-phenylindan (EC 223-467-4, CAS RN 3910-35-8) shows that the dimer fulfils the P/vP criteria of REACH Annex XIII. This dimer was chosen as a potential worst-case representative for the dimer fraction to clarify the P/vP for the group.

No experimental data is available for the trimers. However, (Q)SAR predictions are considered acceptable for the purpose of supporting the read-across hypothesis that the trimer (1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindane) (EC 255-584-1, CAS RN 41906-71-2) is at least as persistent as the dimer (1,1,3-trimethyl-3-phenylindan) (EC 223-467-4, CAS RN 3910-35-8). Based on a read-across from the dimer (1,1,3-trimethyl-3-phenylindan) (EC 223-467-4, CAS RN 3910-35-8) to the trimer (1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan) (EC 255-584-1, CAS RN 41906-71-2), the trimer (EC 255-584-1, CAS RN 41906-71-2) can also be considered to fulfil the P/vP criteria of REACH Annex XIII (degradation half-life in water >60 days).

12.2. Environmental distribution

The current available environmental distribution data and the evaluation by the evaluating MSCA is detailed in Section 3.2 of the SVHC support document[1] and briefly summarized below.

K_{OC} values and Henry's law constants have been estimated for the dimers and trimers in KOCWIN v2.00 by two different estimation methods (Kow and MCI) and in HENRYWIN v3.20 in EPIsuite (US EPA, 2023)). Fugacity level III modelling (EPIweb) was performed for dimers and trimers for two scenarios (1) assuming equal and continuous emissions to water, soil and air and (2) assuming 100% emission to water. Based on the available information, the dimers and trimers have strong adsorptive properties and are expected to be virtually immobile in soil. When released to the environment, they will tend to distribute primarily to soil and/or sediment depending on the release profile.

12.3. Mobility

Not assessed.

12.4. Bioaccumulation

The current available bioaccumulation data and the evaluation by the evaluating MSCA is detailed in Section 3.4 of the SVHC support document[1] and briefly summarized below.

The dimers have estimated log Kow values of 5.9 to 6.4 and the trimers have estimated log Kow values of 9.0 to 9.5 which all exceed the screening criteria for B/vB (Log Kow > 4.5; ECHA, 2023). Bioaccumulation OECD TG 305 data are available the dimer 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene (EC 228-846-8; CAS RN 6362-80-7) and for the Substance. In the bioaccumulation study for the Substance, analytical monitoring was performed for the three dimers and seven potential trimer constituents, including 1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan (EC no.: 255-584-1, CAS RN 41906-71-2).

The evaluating MSCA concludes that based on the available data, the dimers have shown a potential to reach high levels in carp and in fathead minnow, where the bioconcentration factor (BCF) values are above the B criterion (BCF >2000) of REACH Annex XIII. This accumulation is furthermore supported by (Q)SAR predictions. The trimers showed a depuration half-life of 25.8 days and a growth and lipid-adjusted biomagnification factor of

0.137 in fathead minnow. The estimated corresponding BCF value of the trimer 1,3-dimethyl-1-(2-methyl-2-phenyl)propyl-3-phenylindan (EC 255-584-1, CAS RN 41906-71-2) is in the range of 121 - 46,952 depending on the estimation method (most are above 10,000). The trimer EC 255-584-1 is considered to fulfil the vB criterion (BCF > 5000) according to REACH Annex XIII. This trimer is also concluded to be very bioaccumulative based on the Arnot-Gobas bioaccumulation factor (BAF) estimate and is predicted to be the most bioaccumulative of the trimers.

13. Environmental hazard assessment

No chronic studies on aquatic organisms are available for OAPP or any of its constituents. Short-term toxicity studies on algae, daphnia and fish are available for the registered substance and for one of the dimers. The table below summarises the acute toxicity data. Descriptions of each of the studies are included under the following sections.

Table 13.-1 Overview on acute toxicity for the dimers and trimers. T = test data; P = predicted.

ECOTOXICITY DATA				
Group	**Substance**	**Algae (mg/l)**	**Daphnia (mg/l)**	**Fish (mg/l)**
Dimers	1,1,3-trimethyl-3-Phenylindan CAS RN 3910-35-8	T: n.a. P: EC_{50}= 0.17 (ECOSAR)	T: n.a. P: Outside applicability domain (AD) (ECOSAR)	T: n.a. P: Outside AD (ECOSAR)
	1,1'-(1,1-dimethyl-3-methylene-1,3-Propanediyl)bisbenzene CAS RN 6362-80-7	T: E_rC_{50}> 0.06 (*P. subcapitata*) P: Outside AD (ECOSAR)	T: EC_{50} = 0.057 (*D. magna*) P: Outside AD (ECOSAR)	T: LC_{50}> 0.09 (*O. mykiss*) P: Outside AD (ECOSAR)
	1,1'-(1,3,3-trimethylprop-1-ene-1,3-diyl)dibenzene CAS RN 6258-73-7	T: n.a. P: Outside AD (ECOSAR)	T: n.a. P: Outside AD (ECOSAR)	T: n.a. P: Outside AD (ECOSAR)
Trimers		T: n.a. P: Outside AD (ECOSAR)	T: n.a. P: Outside AD (ECOSAR)	T: n.a. P: Outside AD (ECOSAR)

13.1. Aquatic compartment

Fish

Short-term toxicity to fish

Acute toxicity studies on fish are available for the registered substance in the registration dossier. One test has also been conducted by the Japanese Government under their existing chemicals survey on one of the dimers (CAS RN 6362-80-7).

OAPP
An OECD TG 203 (fish, acute toxicity test) with *Danio rerio* is available for OAPP. Due to the low solubility of constituents in the substance, Water Accommodated Fractions (WAF) were prepared with loading rates of 5, 10, 25, 50 and 100 mg/l. The test system is described as semi-static with renewal of test media every 24 hours. Stability of exposure concentrations were assessed by Total Organic Carbon (TOC) analysis. However, this is a non-specific analytical method with limited sensitivity. The results from the study are as follows:

Table 13.1.-2 WAF acute fish toxicity test with *Danio rerio* on OAPP

Nominal loading rate (mg/l)	Cummulative number of deaths			
	24 h	48 h	72 h	96 h
Control	0/7	0/7	0/7	0/7
5	0/7	0/7	0/7	0/7
10	0/7	0/7	0/7	0/7
25	0/7	2/7	4/7	5/7
50	0/7	0/7	2/7	5/7
100	0/7	2/7	7/7	7/7

The LL50 (Lethal Loading with 50 % lethality) in the fish test was determined by using Probit-analysis (Finney-method, lognormal distribution). The nominal LL50 from this study is 25.8 mg/L.

Dimers
One of the dimers, 1,1'-(1,1-dimethyl-3-methylene-1,3 Propanediyl)bisbenzene (CAS RN 6362-80-7) was tested in a 96 hour acute toxicity study with Medaka (*Oryzias latipes*) (Japanese Ministry of the Environment, 2005a). A full review has not been conducted because these reports have not been translated from Japanese. However, many of the study details can be identified since most of the tables in the study reports are provided in English.

Table 13.3.-2 96-hour acute toxicity study with Medaka (*Oryzias latipes*) exposed to 1,1'-(1,1-dimethyl-3-methylene-1,3 Propanediyl)bisbenzene

Nominal concentration (mg/l)	Measured concentration (mg/l)	Cummulative number of deaths			
		24 h	48 h	72 h	96 h
Control	-	0/10	0/10	0/10	1/10
Solvent control	-	0/10	0/10	0/10	0/10
0.04	0.025	0/10	0/10	0/10	1/10
0.055	0.037	0/10	0/10	0/10	0/10
0.075	0.05	0/10	0/10	0/10	0/10
0.1	0.064	0/10	0/10	0/10	0/10
0.14	0.092	0/10	0/10	0/10	0/10

Except for one dead fish in the control group and one dead fish in the lowest exposure group, no mortality was observed. The LC50 (lethal concentration with 50 % lethality) from this study is reported as above 0.092 mg/l.

It is considered doubtful whether a steady state has been obtained between the substance concentration in the test media and in the fish. In addition, a solvent has been used which further introduces some uncertainty about the results of the study. For these reasons, the study is considered unreliable. The (Q)SAR predictions for acute toxicity to fish are outside the applicability domains of the models in ECOSAR and in the Danish (Q)SAR database.

Trimers
No study data on the trimers have been identified in the literature. In addition, the (Q)SAR predictions for acute toxicity to fish are outside the applicability domains of the models in ECOSAR and in the Danish (Q)SAR database.

Long-term toxicity to fish

No information is available in the registration dossier for OAPP or any of its constituents and no chronic fish studies have been identified in the literature.

Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Acute toxicity studies on *Daphnia magna* are available for three different technical products of the registered substance OAPP in the registration dossier. One test has also been conducted by the Japanese Government under their existing chemicals survey on a dimer (CAS RN 6362-80-7).

OAPP
Three OECD TG 202 (*Daphnia magna* acute immobilization) tests are reported in the registration dossier. The tests have been conducted on three different technical products

of OAPP (LA 100, LA 300 and LA 700). These technical products differ in their relative concentration of the different constituents. The tests were conducted with a static test design using WAFs. Five different loading rates were used (5, 10, 25, 50 and 100 mg/l) and 20 test animals were used for each concentration and for the control. The 48 hour EL_{50} values are presented in the table below:

Table 13.4.-3 OECD TG 202 (*Daphnia magna* acute immobilization test) WAF testing

Technical product	EL50 (mg/l)	Remarks
LA 100	17	Based on nominal loading rates
LA 300	14	Based on nominal loading rates
LA 700	51	Based on nominal loading rates

It should be noted that the use of loading rates as reported in this study is not very useful for the purpose of PBT assessment since it is impossible to distinguish the contribution from each constituent to the observed toxicity. Furthermore, since the constituents have very different profiles with regard to e.g. water solubility and log Kow, the composition of the WAF will predominantly consist of those constituents that have the highest solubility in water. For some of the more hydrophobic constituents, chronic studies using a dietary exposure would be needed in order to characterize the aquatic toxicity.

Dimers

One of the dimers, 1,1'-(1,1-dimethyl-3-methylene-1,3 Propanediyl)bisbenzene (CAS RN 6362-80-7) was tested in a 48 hour acute toxicity study with *Daphnia magna* (Japanese Ministry of the Environment, 2005b). A full review has not been conducted because these reports have not been translated from Japanese. However, many of the study details can be identified since most of the tables in the study reports are provided in English.

The study used five different concentrations, a control and a solvent control with 20 animals in each. The results are presented in the table below. The 48 hour EC_{50} value is 0.057 mg/l.

Table 13.5.-4 48-hour acute toxicity study with *Daphnia magna* exposed to 1'-(1,1-dimethyl-3-methylene-1,3 propanediyl)bisbenzene

Nominal concentration (mg/l)	Measured concentration (mg/l)	Cumulative number of immobilized daphnia (percent immobility)	
		24 h	48 h
Control	-	0 (0)	0 (0)
Solvent control	-	0 (0)	0 (0)

0.03	0.023	0 (0)	0 (0)
0.042	0.031	0 (0)	0 (0)
0.06	0.046	0 (0)	4 (20)
0.85	0.064	1 (5)	13 (65)
0.12	0.096	12 (60)	20 (100)

Trimers
No study data on the trimers have been identified in the literature. In addition, the (Q)SAR predictions for acute toxicity to daphnia are outside the applicability domains of the models in ECOSAR and in the Danish (Q)SAR database.

Long-term toxicity to aquatic invertebrates

No information is available in the registration dossier for OAPP and no chronic daphnia studies have been identified in the literature for the registered substance or for any of its constituents.

Algae and aquatic plants

An OECD TG 201 (Alga, Growth Inhibition Test) is reported in the registration dossier. The test was conducted on the technical product LA 700. Nominal loading rates were 5, 10, 25, 50, 100 and 250 mg/L. The test used a static design with a test duration of 72 hours. The EL50 is presented in the table below:

Table 13.6.-5 72-hour algae toxicity study on OAPP

Technical product	EL50 (mg/l)	Remarks
LA 700	EL50 > 250 mg/l (based on growth rate) NOELR = 25 mg/l (based on biomass and growth rate)	Based on nominal loading rates

It should be noted that the use of loading rates as reported in these studies is not very useful for the purpose of PBT assessment since it is impossible to distinguish the contribution from each constituent to the observed toxicity.

Dimers
One of the dimers of C9 monomers 1,1'-(1,1-dimethyl-3-methylene-1,3 propanediyl)bisbenzene (CAS RN 6362-80-7) was tested in a 72 hour toxicity study with *Pseudokirchneriella subcapitata* (Japanese Ministry of the Environment 2005c). The study used a single test concentration of 0.12 mg/L (nominal) / 0.059 mg/L (measured). At the

tested concentration a growth inhibition of 0.9% (growth rate) and 4.3% (biomass) was observed. The EC50 and No observed adverse effect concentration (NOAEC) from this study is >0.059 mg/L (measured) based on growth rate and biomass.

Conclusion on short- and long-term aquatic toxicity

Short-term toxicity tests with OAPP have shown a LL50 of 25.8 mg/L towards fish and an EL50 of 14 mg/L towards aquatic invertebrates while a growth inhibition study have shown an EL50 > 250 mg/L.
One dimer (CAS RN 6362-80-7) has been tested in a fish short-term toxicity study and a 48 hour *Daphnia magna* toxicity study with a LC50 of 0.092 mg/L and an EC50 of 0.057 mg/L, respectively. Similarly, this dimer has shown an EC50 and a NOAEC > 0.059 mg/L in a growth inhibition study using a single test concentration.

Based on the above, it appears that the dimer is more toxic when compared to the whole substance. However, aquatic toxicity studies on the whole substance are not considered very useful as the composition of the WAF will predominantly consist of those constituents that have the highest water solubility. In addition, the low water solubility of most of the constituents limits the relevance of the acute studies. Hence, chronic studies using dietary exposure would be needed in order to characterize the aquatic toxicity. Unfortunately, no long-term toxicity studies are on fish or aquatic invertebrates are available.

13.2. Terrestrial compartment

Not assessed.

13.3. Microbiological activity in sewage treatment systems

An OECD TG 209 (Activated Sludge, Respiration Inhibition Test) has been conducted with OAPP. The 3 h EL_{50} (effect level with 50 % inhibition) is reported as above 100 mg/l WAF (based on respiration rate).

13.4. PNEC derivation and other hazard conclusions

Not assessed.

13.5. Conclusions of the environmental hazard assessment and related classification and labelling

Not assessed.

14. Human health hazard assessment

Evaluation of all human health endpoints was not within the initial concern or scope of this substance evaluation. Information on reproductive toxicity was assessed specifically to determine if the Substance and its relevant constituents have human health endocrine disrupting properties. The assessment of the human health endocrine disrupting properties is documented in Section 15.2 below. Additionally, human health endpoints were assessed to conclude whether the Substance would fulfil the classification criteria for hazard classes relevant to the conclusion on the T criterion in the context of the PBT assessment. Taken together, the available information does not indicate that the Substance (or its constituents) fulfils the T criteria as set out in Annex XIII based on human health hazards.

14.1. Toxicokinetics

Not assessed

14.2. Acute toxicity and Corrosion/Irritation

Not assessed

14.3. Sensitisation

Not assessed

14.4. Repeated dose toxicity

Non-human information

Repeated dose toxicity: oral

A repeated dose toxicity study was performed according to the design and specifications requested by ECHA in the substance evaluation decision issued in 2014, i.e. combining an Extended One-Generation Reproductive Toxicity Study (OECD TG 443; EOGRTS) with a Repeated Dose 90-Day Oral Toxicity Study (OECD TG 408), using the F1 generation of the EOGRTS for the TG 408 study. Hence, exposure in the OECD TG 408 study started *in utero* (via placental transfer), continued throughout weaning (via maternal milk), and further for approximately 100 days in order to evaluate sub-chronic toxicity of the Substance.

The dose levels of OAPP were chosen based on available information from previous experimental work including a preliminary range-finding study and an OECD TG 422 study (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test). In the OECD TG 422 study, OAPP was administered in diet at concentrations of 300, 1250 and 5000 ppm (equivalent to dietary doses of approximately 24, 97 and 338 mg/kg bw/day). Significantly reduced body weights and food consumption was seen in the high doses of both sexes; slight differences were seen in the mid-dose females. Organ weight and macroscopic observations at necropsy showed hepatic enlargement in both sexes at the high-dose and in mid-dose males. Hence, the selection of doses for the combined OECD TG 443/408 study was 0, 150, 500, or 1500 ppm in diet. In the parental males, this corresponded to doses of approximately 0, 10, 30 and 90 mg/kg bw/day and in the dams, this was equivalent to 0, 14, 47 and 150 mg/kg bw/day when calculated over the entire dosing period. When calculated for both sexes and both generations, across all time periods, the mean doses were 0, 12, 40, and 124 mg/kg bw/day.

In Part 1 of the study (EOGRTS), the Substance was administered continuously in the diet to male rats (n=24) for a period of 10 weeks (pre-mating), through the mating period and after, for a total of at least 13 weeks. Female rats (n=24) were treated for 10 weeks pre-mating and during the mating, gestation and lactation periods for a total of at least 16 weeks of treatment. At weaning (around postnatal day (PND) 21), male and female pups were randomly assigned to one of three cohorts of animals and treated for approximately 100 days:

- subset 1 (cohorts 1A and 1B) = Reproductive/developmental toxicity testing. Cohort 1A was also used for Part 2 (the OECD TG 408). In cohort 1B, 5 animals /sex/dose from the control and the high-dose group, were used for recovery testing. These animals were kept on control-group diet for 30 additional days after the treatment had finished
- subset 2 (cohorts 2A and 2B) = Developmental neurotoxicity testing, 2A (neurobehavioral testing), 2B (neurohistopathology assessment)
- subset 3 (cohort 3) = Developmental immunotoxicity testing

Necropsy and macroscopic examinations were performed on all surviving animals at the end of the treatment period. Animals from cohorts 2A, 2B, and Cohort 3 were treated the same way as OECD TG 408 (Cohort 1A or "Part 2") animals.

Cohorts 1A and 1B are described in the following while Cohorts 2A, 2B and 3 are described in section 14.7.

In the parental generation, minor clinical signs were detected in some animals and one high-dose animal was found dead on day 36. These effects are not considered to be related to treatment. In both sexes, at treatment-related decrease in mean body weight and body weight gain was observed in the high-dose group. Decreased body weight and weight gain was also observed in the mid- and low-dose groups but this was not statistically significant.

After weaning of the pups, no mortalities and no adverse clinical signs were seen in the cohort 1A animals used for testing of repeated dose toxicity. Both male and female pups in the high-dose group were significantly smaller than controls at the time of weaning (~ 10%). In the high-dose males, the lower body weight persisted throughout the study with a statistically significant (~7%) lower body weight seen on PND 120. Terminal body-weight gains (PND 21-120) were 6.5 % lower for high-dose males, but remained statistically insignificant. The terminal mean body weights of mid- and high-dose females also remained significantly lower throughout the study, compared with those of the controls (-9 and -18 %, respectively), with corresponding decreases in body-weight gains (-10% and -20%, from PND 21-120, respectively). These decreases in mean body weight in the male and female groups were considered to be treatment-related.

There were no adverse effects on haematology or clinical chemistry in any group of Cohort 1A or 1B. Reductions in some organ weights (including thymus, spleen, heart, kidney, prostate and ovaries) were observed. These differences were considered to be secondary to the body weight effect as the effects were mainly seen for organ weight changes relative to body weight and histopathological examinations showed no treatment-related effects.

A statistically significant treatment-related liver weight increase was observed in both sexes in the high-dose group and to a slight extent in mid-dose males. In high-dose males, absolute liver weights were 20% increased and relative liver weights were 29.6% increased. In the female offspring, the effects were non-significant on absolute liver weight, whereas relative liver weights were 15% increased. Liver histopathology revealed treatment-related mixed form of hepatocellular vacuolation in the high-dose males and females, visualised as pale lobes in some males at necropsy. Centrilobular and periportal zonation were seen and the severity varied from minimal to moderate in both male and female offspring. The changes (qualitatively and quantitatively similar to F0 generation) were considered non-adverse hepatic changes.

In the recovery animals of the 90-day toxicity study part (cohort 1B), there were no statistically significant differences in liver weights and no treatment-related macroscopic or microscopic hepatic changes in examined males and females after the recovery period. This was considered to confirm the non-adverse nature of the terminal hepatic observations.

Overall, the study revealed that exposure to OAPP for 100 days in offspring and adult animals did not result in any specific target organ toxicity arising from repeated exposure.

14.5. Mutagenicity

The only genotoxicity study available with the Substance is an Ames study (OECD TG 471). A positive response is observed in one strain (TA 100) with metabolic activation but only at cytotoxic concentrations. The other tested strains were negative. Other standard information requirements for mutagenicity were filled by the use of read across to structural analogues.

Mammalian cell gene mutation studies (OECD TG 476) are reported for two analogue substances (phenol, styrenated and hydrocarbons, C9-unsaturated, polymerised). An *in vitro* mammalian chromosome aberration test (OECD TG 473) is reported for the analogue substance hydrocarbons, C9-unsaturated, polymerised. Finally, an *in vivo* micronucleus assay (OECD TG 474) is available for the analogue substance phenol, styrenated. All studies are negative for genotoxicity.

Based on the above and on the applied read across and additional (Q)SAR estimations for mutagenicity for the individual constituents (which are all negative and within applicability domain of the models), the evaluating MSCA concludes that there is currently no concern for mutagenicity.

14.6. Carcinogenicity

Not assessed.

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

Effects on fertility

Fertility was assessed in a combined OECD TG 443 with OECD TG 408 as described in section 14.4.

In the parental (F0) generation, no adverse clinical signs of toxicity were observed, and the evaluated haematology and clinical chemistry parameters were unaffected by treatment. Treatment-related decreases in body weight and body weight gain were seen in the high-dose animals of both sexes. In parental animals from the highest dose group, a reduction in body weight of 9% and a reduction in body weight gain of ~15% was seen on days 71 and 95 of the study. In the dams, body weights in the highest dose group were 9.4% lower on day 71 and body weight gain was 24.7% lower at this time point. During the gestation period and on PND 1, high-dose females had around 10% lower body weight and body weight gain, compared to controls. Decreases in body weight also occurred in the mid- and low-dose parental groups but rarely more than 5% and the changes were without clear trends and in most cases without statistical significance.

Alterations in some relative reproductive organ weights were observed in the high-dose parental animals of both sexes. However, these were likely a consequence of lower body weights and not an adverse effect and histopathology showed the organs to be normal.

No treatment-related changes were seen in reproductive parameters during mating and gestation, delivery or post-partum/lactation periods in any of the treatment groups.

Maternal animals showed no signs of altered oestrus cyclicity due to test substance exposure during the 10-week premating period. There were no effects of treatment observed on F1 offspring viability and no clinical signs. In addition, gross necropsy did not reveal any remarkable findings. At birth and during the postnatal period up until weaning on PND 22, offspring body weights were unaffected by exposure to the test substance.

Based on an overall evaluation of the requested data, no indications of adverse effects of OAPP on fertility were observed.

Developmental toxicity

Developmental toxicity was assessed in a combined OECD TG 443 with OECD TG 408 described in section 14.4.

There were no effects of treatment observed on F1 offspring viability, clinical signs, or development and gross necropsy did not reveal any remarkable findings. At birth and during the postnatal period up until weaning on PND 22, offspring body weights were unaffected by exposure to the test substance.

As specified in OECD TG 443, anogenital distance (AGD) was assessed in all offspring on PND 0 and nipple retention (NR) was assessed in all offspring on PND 12/13. No significant effects were seen on these two endpoints in either male or female offspring.

It should be noted that data for NR do not seem to have been assessed reliably, as all male offspring had zero nipples and all females had 12. As some biological variation always exists when assessing this endpoint, this questions the quality of the recording for this endpoint. However, no indications of effects were seen on AGD determination and no adverse treatment-related effects were seen on any other male reproductive endpoints (as described in more detail below).

Vaginal patency was evaluated daily for each weaned female, beginning on PND 22 and ending on PND 34 and oestrous cycles were monitored in female offspring for the two weeks following vaginal patency. Weight and histopathology of ovaries and uterus with cervix was assessed in adult female offspring. Furthermore, in the adult female offspring from the control and high-dose group, detailed histological examination of the ovaries was performed. This covered the follicular, luteal and interstitial compartments of the ovary as well as the epithelial capsule and ovarian stroma and a qualitative depletion of the primordial and small growing follicles as well as corpora lutea in the ovaries of Cohort 1A. None of these endpoints were significantly affected by the Substance.

Reproductive endpoints were also assessed in the male rats according to the requirements of OECD TG 443. All F1 males were evaluated for balanopreputial separation (sexual maturation) daily beginning on PND 35 to detect age of sexual maturation. In the parental male animals and in adult male offspring, the following organ weights were weighed and examined histologically at study termination: prostate, testis, epididymides, seminal vesicles and pituitary. Furthermore, detailed testicular histopathological examination was conducted to identify treatment-related effects such as retained spermatids, missing germ cell layers or types and multinucleated giant cell. Examination of the epididymis included evaluation of the caput and cauda using longitudinal sectioning. Additionally, sperm motility, morphology and sperm count were assessed in parental males and in male offspring from cohort 1A. Apart from a few significant changes in relative weight of some of the organs, which were most probably caused by reductions in terminal body weight, none of the male reproductive endpoints were significantly affected by OAPP exposure.

Reductions in some relative organ weights were also observed in the high-dose parental animals of both sexes. However, these were likely a consequence of lower body weights and not an adverse effect and histopathology showed the organs to be normal.

No treatment-related changes were seen in reproductive parameters during mating and gestation, delivery and post-partum/lactation periods in any of the treatment groups.

Based on an overall evaluation of all the requested data, no indications for developmental toxicity of OAPP were observed.

Developmental Neurotoxicity

Developmental neurotoxicity was investigated in the previously described combined OECD TG 443/408 EOGRTS study. The animals in Cohort 2A were used for neurobehavioural testing and for neuropathological assessment in adulthood. At least 10 animals/sex/dose were investigated.

There were no mortalities after weaning and no adverse clinical signs. An auditory startle reflex test (50 stimuli per animal with pseudorandom intervals per animal) was performed on PND 24 or PND 25. At the age of both 2 and 3 months, a functional observational battery (FOB) test was performed which included measurement of grip strength, a splay test and a one-hour test of locomotor activity. None of these endpoints showed any dose-related effects of the Substance. At the age of 75-90 days, necropsy (with perfusion) was performed. There were no adverse effects on brain weight and no treatment-related findings observed in detailed histopathological examination of the central nervous system (CNS) and peripheral nervous system (PNS) of examined animals in the high-dose group.

Brain morphometry was investigated in the control group and high-dose group. The brain was processed to wax blocks and three consecutive sections were taken at landmarks (level) 3, 4 and 7. The slides were digitalized and the most homologous and representative sections for the specific brain areas were selected. The appropriate relative dimensions of the cerebral cortex, hippocampus and cerebellum were assessed. Most of the measured endpoints showed no adverse substance related effects but hippocampus thickness in high-dose males and cornu Ammonis thickness in high-dose females were significantly decreased. However, the changes were only observed unilaterally. Therefore, a relationship to treatment was by the study authors considered to be unlikely and was explained as related to variability in the section processing/measuring. The evaluating MSCA finds this explanation plausible.

Cohort 2B from the previously described combined OECD TG 443/408 study was assigned for neurohistopathological assessment at weaning (PND21/22) (with perfusion). 10 animals/sex/dose were used. Brain histopathology was performed for all control- and high-dose animals. No mortalities after weaning, no adverse clinical signs, no significant body- or organ weights difference were seen in this study. Moreover, no treatment-related macroscopic changes in any organs or tissues and no histopathological changes in the CNS of the examined animals in the high-dose group were seen. Brain morphometrics (assessed in Control and high-dose animals) showed no differences between groups.

Based on an overall evaluation of all the requested data, no signs of developmental neurotoxicity of OAPP were observed.

Developmental immunotoxicity

Investigation of developmental immunotoxicity was performed in cohort 3 of the previously described combined OECD TG 443/408 study. At least 10 animals/sex/dose were investigated. In addition, Cohort 1A animals were subjected to extra immunotoxicity steps at termination, including weighing of extra organs/tissues associated with the immune system and analysis of splenic lymphocyte subpopulations (immunophenotyping). The immunophenotyping analysis was conducted to determine the relative and absolute counts of six different lymphocyte subpopulations and indicated that there was no shift in the immunological steady state distribution of "helper" (CD4+) or cytotoxic (CD8+) thymus derived lymphocytes or natural killer cells, related to the treatment. In case of absolute counts, no statistical difference was observed between treated groups and the control group for any parameters in either sex. In case of relative counts, the Dunnett’s post-hoc test revealed no statistically significant differences between treated and control groups for any parameters in either sex.

In Cohort 3, macroscopic evaluation did not show any abnormalities: spleen, thymus, femur with bone marrow, sternum with bone marrow, axillary and mesenteric lymph nodes, Peyer’s patches were normal in all Substance-treated groups. In the functional immunological assessment (T-cell dependant antibody response assay), treatment with the positive control substance (cyclophosphamide) gave the anticipated strong inhibitory response: the decrease in the anti Sheep Red Blood Cell Immunoglobulin M (SRBC IgM) level of the positive control animals compared to the negative control group was statistically significant in male and female animals thus indicating impairment of the functional immune response.

In the developmentally exposed males, no statistically or biologically significant changes were detected in the anti SRBC IgM levels. In female offspring, some statistically significant differences including decreased anti SRBC IgM levels compared to the negative control group were detected in high-dose groups of the female animals. According to the study author, the Substance did not exhibit any immunotoxic effects. However, the evaluating MSCA concludes that this may by a treatment-related finding.

14.8. Hazard assessment of physicochemical properties

Not assessed.

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

Not assessed.

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

In the requested combined repeated dose toxicity study and extended one generation reproductive toxicity (EOGRTS) (OECD TG 408/443) study, the top dose (1500 ppm corresponding to ~124 mg/kg bw/day) caused significant and consistent reductions in parental and offspring body weights in both sexes. At sacrifice, parental animals showed a reduction in body weight gain of ~15 & 25% (males and females, respectively). In the offspring at the time of weaning, both high-dose male and female offspring were significantly smaller than controls (~10%) and this lower body weight persisted throughout the study resulting in a 7% and 18 % lower body weight at termination on PND 120. The livers of the exposed animals were also affected in both generations with parental animals showing an increase in absolute liver weights of 11-19% and relative liver weight increases of ~23 %. In the offspring, similar effects were seen with high-dose males showing 20% increase in absolute and 30% increase in relative liver weight. Liver histopathology was also affected and the severity of the effects ranged from minimal to moderate in high-dose parental males and minimal to severe in high-dose parental females. The histopathological changes were qualitatively and quantitatively similar in the F1 generation. These liver- and body weight changes indicate that higher doses would not have been appropriate to use in this study.

The evaluating MSCA assessed the requested combined repeated dose toxicity and extended one generation reproductive toxicity to determine if the Substance fulfilled the classification criteria for toxicity to reproduction, which would link to the T criterion in the PBT assessment. Based on the available data, the evaluating MSCA concludes that the Substance does not fulfil the classification criteria for reproductive toxicity or STOT RE.

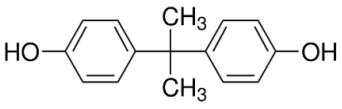
15. Endocrine disrupting (ED) properties assessment

OAPP has been assessed for ED effects relevant for both human health and the environment. As described below, especially the phenolic fraction of OAPP is known to have the potential to interact with the endocrine system.

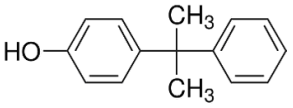
15.1. Endocrine disruption – Environment

Monoalkylated phenol

The constituent 4-(α,α-dimethylbenzyl)phenol (CAS RN 599-64-4) is structurally very similar to Bisphenol A (BPA), the only difference being an additional OH group attached to the second benzene ring in BPA.



Bisphenol A
(BPA)



4-(α,α-dimethylbenzyl)phenol
(p-Cumylphenol)

Biggers and Laufer (2004) tested the juvenile hormone (JH) activity of different alkyl phenols in an assay based on their effects on the settlement and metamorphosis of larvae of the polychaete *Capitella*. In this sensitive assay, 4-(α,α-dimethylbenzyl)phenol showed high JH activity (EC_{50} of 3 µM), while another constituent 2,4-bis(1-methyl-1-phenylethyl)phenol (CAS RN 2772-45-4) also showed high JH activity (EC_{50} of 2 µM) and whereas BPA showed very high activity (EC_{50} of 0.05 µM).

Terasaki *et al*. (2005) measured the affinity to estrogen receptors of 10 compounds found as impurities in industrial grade bisphenol A (BPA) by yeast 2-hybrid assays incorporating the human estrogen receptor (hER) or the medaka fish (*Oryzias latipes*) estrogen receptor (mER). Five impurities showed greater activity than BPA itself in an agonist assay for hER. The constituent of OAPP, 4-(α,α-dimethylbenzyl)phenol (CAS RN 599-64-4), was the most active of the impurities in the hER assay. It was 12 times as active as BPA in the assay incorporating the human estrogen receptor and 6 times as active in the assay incorporating the medaka estrogen receptor.

Sanseverino *et al.* (2009) screened the estrogenic and anti-androgenic hormone activity in a bioluminescent yeast bioreporter assay. 4-(α,α-dimethylbenzyl)phenol was found to display estrogenic activity with a higher relative potency (a factor of 3) than BPA. No anti-androgenic activity was observed for 4-(α,α-dimethylbenzyl)phenol.

(Q)SAR models in the Danish (Q)SAR database predict that 4-(α,α-dimethylbenzyl)phenol and dialkylated phenol (CAS RN 2772-45-4) will bind to the estrogen receptor. For 4-(α,α-dimethylbenzyl)phenol, receptor activation is also predicted. These predictions are within the structural applicability domain of the model and supported by the OECD (Q)SAR Toolbox profilers (Danish (Q)SAR Database, 2019).

In the requested OECD TG 305 study with additional VTG measurements, male fish showed significantly increased VTG induction compared to controls when exposed to the Substance for 14 days.

In the registration dossier, a read-across is applied from 4-monostyrenated phenol (EC 217-864-1; 4-MSP, source substance) to 4-(α,α-dimethylbenzyl)phenol (target substance) based on a positive FSDT (OECD TG 234). According to the evaluating MSCA, the results on VTG and sex ratio in the FSDT study confirm the estrogenic agonism of 4-MSP and can be utilized to conclude on 4-(α,α-dimethylbenzyl)phenol.

The test substance concentrations used in the FSDT were based on a 21-d range-finding Fish, Early-life Stage (FELS) toxicity test (OECD TG 210) at 0.02, 0.2 and 2 mg/L, with 100 % mortality at the highest concentration and no effects at 0.2 mg/L. In the FSDT, five concentrations were tested: 0, 2.1, 6.4, 19.7, 61.8 and 187.9 µg/L with 4 replicates (30 eggs). The study was conducted as a flow-through setup without the use of solvent and with a duration of 63 days post fertilization. VTG significantly increased in females in the highest test concentration of 187.9 µg/L. The result on the apical endpoint sex ratio was clear with no males out of 94 examined fish in the highest test concentration and a clear dose-related increase in stage 0 females with a NOEC of 2.1 µg/L. These results confirm the endocrine mode of action and endocrine-specific population-relevant effects as a change in sex ratio occurring without systemic toxicity is both endocrine-specific and adverse. All validity criteria as specified in the test guideline were met and the study is considered valid and reliable without restriction.

The evaluating MSCA concludes that the available data indicate that the Substance acts as an endocrine disruptor for the environment.

15.2. Endocrine disruption – Human health

As described in the previous section, the Substance constituent 4-(α,α-dimethylbenzyl)phenol (CAS RN 599-64-4) has been investigated for its endocrine disrupting properties in several *in vitro* studies. The constituent has been shown to be significantly more active than BPA in a yeast 2-hybrid assay, incorporating the human estrogen receptor (hER) (Terasaki *et al*., 2005) and in a bioluminescent yeast bioreporter assay (Sanseverino *et al.,* 2009). It has also been shown to bind strongly to the human estrogen-related receptor gamma (ERRgamma) (Matsushima *et al*., 2008) and to have estrogen agonist activity in an assay using the human ovarian cancer cell line, BG-1, that expresses both human hER-alpha and hER-beta (Casey *et al.,* 2010). Okuda *et al.* (2011) furthermore tested the estrogenic activity of this constituent and of BPA in a yeast estrogen screening assay after incubation with rat liver S9 fraction. BPA exhibited an increase of estrogenic activity after incubation with S9, whereas the estrogenic response of this constituent was almost lost after incubation with S9, indicating that metabolic transformation of this compound in the rat liver may render it inactive in relation to the *in vitro* estrogenic properties of the parent compound.

No anti-androgenic activity was observed for 4-(α,α-dimethylbenzyl)phenol in a bioluminescent yeast bioreporter assay (Sanseverino *et al.,* 2009).

No *in vitro* studies investigating endocrine disrupting properties have been identified for the Substance. Hence, assessment of its endocrine disrupting properties has been performed based solely on *in vivo* results from the combined OECD TG 443/OECD TG 408. The study design has been described in detail in the previous sections, but the results which are relevant for assessing endocrine disruption are summarised below.

No significant effects on AGD or NR were seen in either male or female offspring. Because estrogenic activity was suspected based on previous (Q)SAR and *in vitro* results, effects on female reproductive endpoints were of special interest in relation to the endocrine disrupting potential of the Substance. In the performed study, these included oestrous cycling, weight and histopathology of uterus and ovaries in dams and offspring as well as timing of vaginal patency (sexual maturation) in the offspring. However, none of these endpoints were significantly affected by the Substance.

Reproductive endpoints were also assessed in the male rats according to the requirements from the OECD TG 443. All F1 males were evaluated for balanopreputial separation (sexual maturation) daily beginning on PND 35 to detect age of sexual maturation. In the parental male animals and in adult male offspring the following organ weights were weighed and examined histologically at study termination: prostate, testis, epididymides, seminal vesicles and pituitary. Furthermore detailed testicular histopathological examination was conducted to identify treatment related effects such as retained spermatids, missing germ cell layers or types, and multinucleated giant cell. Examination of the epididymis included evaluation of the caput and cauda using longitudinal sectioning. Additionally, sperm motility, morphology and sperm count were assessed in parental males and in male offspring from cohort 1A. Apart from a few significant changes in relative weight of some of the organs, which were most probably caused by reductions in terminal body weight, none of the male reproductive endpoints were significantly affected by OAPP exposure.

Based on an overall evaluation of all the above-mentioned measurement, no indications of anti-androgenic or estrogenic effects of OAPP were observed.

Thyroid endpoints were also assessed in the OECD TG 443 study. T4 hormone levels in plasma from parental animals and from offspring on PND 4 and PND 21 and in adulthood (cohort 1A) were unaffected by OAPP exposure. Thyroid-stimulating hormone (TSH) levels were not assessed in PND4 offspring and were below level of detection in 87% of the

offspring plasma samples on PND22 (equally distributed throughout dose groups). In parental animals and in adult offspring from cohort 1a, TSH levels seemed increased (30-40% increase in high-dose males and 20-25 % increase in high-dose females compared to controls) but these increases were not statistically significant because of the large variation in the data. As no other indications of adverse effects on the thyroid hormone system were seen (i.e. no effect on thyroid gland weight or histopathology), it is likely that OAPP did not affect the thyroid hormone system of the rats.

The overall evaluation is that no indications of anti-androgenic or estrogenic effects of OAPP were observed in rats. Also, no signs of developmental neurotoxicity (DNT cohort) or of repeated dose toxicity were observed. The registered substance is not assessed to give rise to effects on fertility or development in mammalians.

For the pre-natal developmental toxicity study (OECD TG 414), no effects were observed at 60,150 or 400 mg/kg/d besides mild maternal toxicity.

The evaluating MSCA concludes that based on the available data, the Substance is not a human health endocrine disruptor.

15.3. Conclusions of the endocrine disrupting properties assessment and related classification and labelling

The evaluating MSCA concludes that based on the available data and in accordance with the CLP EU No 1272/2008 Regulation, the Substance meets the criteria for classification as an endocrine disruptor for environment but does not meet the criteria for classification as an endocrine disruptor for human health.

16. PBT/vPvB assessment

16.1. Persistence

The available data for persistence are detailed in Section 3.1 of the available SVHC support document[2]. Based on the available data, the evaluating MSCA concludes that:

- Very limited biodegradation was observed in an OECD TG 310 ready biodegradation study with OAPP. However, ready biodegradation tests are not capable of discriminating between the relative degradation of each of the constituents and it is hypothesized that strong sorption of some of the lipophilic constituents may reduce the bioavailability to degrading microorganisms.
- A dimer constituent screen as potentially P or vP based on a ready biodegradability test equivalent to OECD TG 301C. Furthermore, reliable (Q)SAR predictions for biodegradation indicate that all dimers screen as potentially P or vP.
- The potential worst-case dimer (CAS RN 3910-35-8) showed that after 60 days, 11.2% and 10.6% mineralization was reached for the 1 and 10 µg/L concentrations, respectively in an OECD TG 309. The study indicates that the dimer fulfils the P/vP criteria with a half-life in freshwater ≥205 days.
- As regards the trimers, reliable (Q)SAR predictions for biodegradation indicate that all the trimer constituents screen as potentially P or vP. No experimental data is available for the trimers. Based on a read-across approach with the dimer, it can be reasonably assumed that the trimer is at least as persistent as the dimer.

[2] https://www.echa.europa.eu/documents/10162/6c4b3401-858d-0b65-e5b1-1484fce3c84c

Since OAPP contains both dimers and trimers with P/vP properties, it is concluded that OAPP meets both the P and vP criteria in accordance with Annex XIII of the REACH Regulation.

16.2. Bioaccumulation

The available data for bioaccumulation are detailed in Section 3.4 of the available SVHC support document[3]. Based on the available data, the evaluating MSCA concludes that:

- The dimers and trimers both screen as potentially B and vB with log Kow values > 4.5 based on (Q)SAR estimates.
- The dimers have shown a potential to reach high levels in fish where the BCF values in the range 499–4608 have been observed depending on the estimation method.
- As regards the trimers, data on the whole substance indicate BCF values above 10,000 (values in the range of 66.5-55,987 depending on the estimation method).
- Reliable (Q)SAR) predictions for one trimer have shown a BAF of 177,800. The trimers are therefore considered to fulfil the vB criterion of REACH Annex XIII (BCF > 5000).

Since OAPP contains trimer constituents with B/vB properties at a concentration ≥ 0.1 % (w/w), it is concluded that OAPP meets the B and vB criteria in accordance with Annex XIII of the REACH Regulation.

16.3. Mobility

Not assessed.

16.4. Toxicity

The available information indicates that the Substance is unlikely to meet the T criteria based on relevant human health hazards. However, it is not possible to derive a firm conclusion for the T criteria as no chronic studies on aquatic organisms are available for OAPP or any of its constituents.

16.5. Conclusions of the PBT/vPvB assessment and related classification and labelling

The Substance is identified as a vPvB substance according to Art. 57(e) of REACH.

17. Exposure assessment

Not assessed.

18. Risk characterisation

Not assessed.

[3] https://www.echa.europa.eu/documents/10162/6c4b3401-858d-0b65-e5b1-1484fce3c84c

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20. Abbreviations

4-MSP	4-monostyrenated phenol
AD	Applicability domain
AGD	Anogenital distance
B	Bioaccumulative
BCF	Bioconcentration factor
BPR	Biocidal products regulation (EU) 528/2012
BAF	bioaccumulation factor

BCF	bioconcentration factor
BPA	Bisphenol A
BPR	Biocidal products regulation (EU) 528/2012
CAS RN	CAS registry number
CCH	Compliance check
CLH	Harmonised classification and labelling
CLP	Classification, labelling and packaging
CNS	Central nervous system
CoRAP	Community rolling action plan
DIT	Developmental immunotoxicity
DMEL	Derived minimal effect level
DNEL	Derived no-effect level
DNT	Developmental neurotoxicity
EC	European community
EC50	Effective concentration with 50 % effect
ECHA	European chemicals agency
ED	Endocrine disruption
EL50	Effect level with 50 % inhibition
EOGRTS	Extended one-generation reproduction toxicity study
EU	European union
FELS	Fish, early-life stage
FOB	Functional observation battery
FSDT	Fish sexual development test
GMT	Group management team
hER	Human estrogen receptor
JH	Juvenile hormone
Koc	organic carbon/water partition coefficient
Kow	n-octanol/water partition coefficient
LC50	Lethal concentration with 50 % lethality
LL50	Lethal loading with 50 % lethality
MSCA	Member state competent authority
n.a.	Not applicable
NOELR	No observed effect level (growth rate)
NOAEC	No observed adverse effect concentration
NONs	Notification of new substances
NR	Nipple retention
OAPP	Oligomerisation and alkylation reaction products of 2-phenylpropene and phenol
OECD	Organisation for Economic Cooperation and Development
P	Persistent
PBT	Persistent, bioaccumulative and toxic
PND	Postnatal day
PNEC	Predicted no-effect concentration
PNS	Peripheral nervous system
POP	Persistent organic pollutants
PPM	Parts per million
PPP	Plant protection products regulation EC 1107/2009
(Q)SAR	Quantitative structure-activity relationship
REACH	Regulation No 1907/2006 concerning registration, evaluation, authorisation, and restriction of chemicals
RAR	Risk assessment report
SRBC IgM	Sheep red blood cell immunoglobulin M
STOT RE	Specific target organ toxicity – repeated exposure
SVHC	Substance of very high concern
TBD	To be decided
TG	Test guideline
TOC	Total organic carbon

TPE	Testing proposal examination
TSH	Thyroid-stimulating hormone
UNEP	United nations environment program
UVCB	Unknown or variable composition, complex reaction products or of biological materials.
vB	Very bioaccumulative
vP	Very persistent
vPvB	Very persistent and very bioaccumulative
VTG	Vitellogenin
WAF	Water accommodated fraction