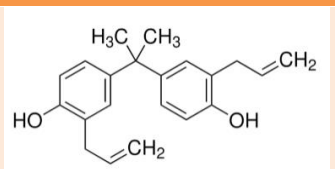
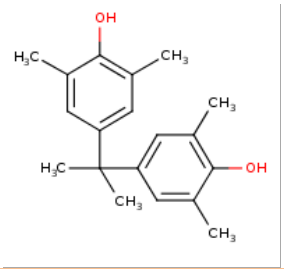
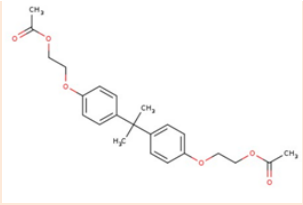
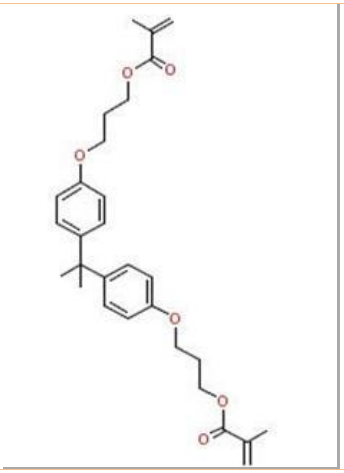
Danish Ministry of the Environment
Environmental Protection Agency

Justification Document for the Selection of CoRAP Substances

EC/List number	CAS RN	Public Substance name	Chemical structure	Registration type
217-121-1	1745-89-7	4,4'-isopropylidenebis[2-allylphenol]		Full
227-033-5	5613-46-7	4,4'-isopropylidenedi-2,6-xylol		Full
242-895-2	19224-29-4	2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bisethyl diacetate		Full

248-607-1	27689-12-9	(1-methylethylidene)bis(4,1-phenyleneoxy-3,1-propanediyl) bismethacrylate		Full

Authority: Denmark

Date: 29 April 2024

Revision history

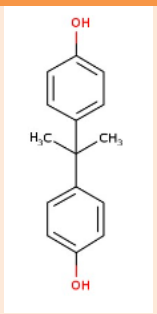
Version	*Date*
1.0	19 March 2024
1.1 (correction of chemical structure for EC/List number 217-121-1)	29 April 2024

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

1. Background

1.1 Analogue substances

EC/List number	CAS RN	Public Substance name	Chemical structure
201-245-8	80-05-7	4,4'-isopropylidenediphenol	

ECHA has grouped together structurally similar substances based on the presence of the 'bisphenol' moiety. Based on the hazard and use screening, ECHA has published an Assessment of Regulatory Needs (ARN) on a group of 'Bisphenols' in 2021[1].

The substances (EC 217-121-7, 227-033-5, 242-895-2 and 248-607-1) nominated for inclusion in the CoRAP all have structural similarities with 4,4'-isopropylidenediphenol (EC 201-245-8), i.e. bisphenol A (BPA). These substances belong to Subgroup of BPA and BPA derivatives in the ARN report.

BPA has been identified as a substance of very high concern as it is toxic for reproduction and an endocrine disruptor for human health and the environment. ECHA has recommended BPA for inclusion in Annex XIV of REACH ('Authorisation List'). Furthermore, the use of BPA in thermal paper is restricted under REACH.

1.2 Overview of ongoing or completed other REACH and CLP processes & other EU legislation

EC/ List number	Evaluation			CLH	Restriction	Authorisation
	CCH	TPE	Previously on CoRAP	Annex VI (CLP)	Annex XVII*	Candidate List/ Annex XIV
217-121-1	-	-	-	-	-	-
227-033-5	-	-	-	-	-	-
242-895-2	-	-	-	-	-	-
248-607-1	-	-	-	-	-	-

**Some of the broad restriction entries in the Annex XVII of REACH are not represented in the overview, e.g. when the scope of the restriction is defined by its classification or the substance identification is broad (e.g. entries 3, 28-30 and 40)*

[1] https://echa.europa.eu/documents/10162/ff076a71-d5a8-0166-17f0-7bd9d42accae

EC/ List number	Other EU legislation PPP/ BPR	Previous legislation NONS/ RAR	Stockholm convention POP	Other (e.g. UNEP)
217-121-1	-	-	-	-
227-033-5	-	-	-	-
242-895-2	-	-	-	-
248-607-1	-	-	-	-

2. Classification

You can find information on classification in the ECHA C&L Inventory database, which includes both harmonised classification (when available) and the notified self-classifications. (http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database]. The CLP Regulation and all published ATPs are available on ECHA website: http://echa.europa.eu/web/guest/regulations/clp/legislation.

EC/ List No	CAS RN	Public Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications (*)
217-121-1	1745-89-7	4,4'-isopropylidenebis[2-allylphenol]	-	Skin Corr. 1B; H314 Skin Sens. 1B, H317 Eye Dam. 1; H318 Aquatic Acute 1; H400 Aquatic Chronic 1; H410	Skin Corr. 1C; H314 (74) Skin Corr. 1B; H314 (75) Skin Sens. 1B, H317 (81) Skin Sens. 1, H317 (53) Eye Dam. 1; H318 (80) STOT SE 3; H335 (14) Repr. 2; H361 (1) Aquatic Acute 1; H400 (95) Aquatic Chronic 1; H410 (95) Not classified (4)
227-033-5	5613-46-7	4,4'-isopropylidenedi-2,6-xylol	-	Aquatic Acute 1; H400 Aquatic Chronic 1; H410	Skin Irrit. 2; H315 (39) Eye Irrit 2; H319 (39) STOT SE 3; H335 (38) Aquatic Aqute 1; H400 (1) Aquatic Chronic 1; H410 (1) Not classified (1)
242-895-2	19224-29-4	2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bisethyldiacetate	-	Not classified	Not classified (1)
248-607-1	27689-12-9	(1-methylethylidene)bis(4,1-phenyleneoxy-3,1-propanediyl) bismethacrylate	-	Aquatic Chronic 4; H413	Aquatic Chronic 4; H413 (1)

(*) the number in brackets indicates the number of notifications received. Each notification can represent a group of notifiers. Therefore the number may differ from the C&L inventory which displays number of notifiers.

3. Tonnage and uses

3.1 Aggregated Tonnage

EC/ List No	Aggregated tonnage (as per ECHA dissemination website*)[2,3]
217-121-1	≥ 100 to < 1 000 tonnes
227-033-5	≥ 10 to < 100 tonnes
242-895-2	≥ 1 to < 10 tonnes
248-607-1	≥ 1 to < 10 tonnes

** The total tonnage band has been calculated by excluding the intermediate uses,- See also the Manual for Dissemination and Confidentiality under REACH (section 2.6.11): https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0*

3.2 Overview of the Uses

Main types of applications	EC 217-121-1	EC 227-033-5	EC 242-895-2	EC 248-607-1
Industrial use	+	+	N/A	N/A
Professional use	N/A	N/A	+	+
Consumer Use	N/A	N/A	N/A	N/A
Article service life	N/A	+	+	+
Formulation	+	N/A	+	+

N/A: no public data indicating whether or in which chemical products the substance might be used, or into which articles the substance might have been processed.

EC 217-121-1 has industrial uses in polymers for manufacture of plastics and formulation uses in adhesives, sealants and polymers. Its release to the environment can occur during formulation of mixtures and thermoplastic manufacture. EC 227-033-5 has industrial uses. Release to the environment can occur from thermoplastic manufacture. According to ECHA's ARN report on bisphenols[4], it also has article service life uses and it is used in the manufacture of polymers, polymer resins and epoxy resins and possibly also as a flame retardant in polymer articles.

EC 242-895-2 and EC 248-607-1 have widespread professional uses and are used in formulation of mixtures. According to ECHA's ARN report on bisphenols[5], they also have article service life uses and they are used in dental sealants.

[2] The total aggregated tonnage band may be available on ECHA's webpage at https://echa.europa.eu/information-on-chemicals/registered-substances
[3] Substance Infocard on ECHA's dissemination website accessed on 6 September 2023. NB. REACH registration data on ECHA's webpage has not been updated since 19 May 2023.
[4] https://echa.europa.eu/documents/10162/ff076a71-d5a8-0166-17f0-7bd9d42accae
[5] https://echa.europa.eu/documents/10162/ff076a71-d5a8-0166-17f0-7bd9d42accae

4. Justification for inclusion on the CoRAP

4.1 Legal basis

☒ Article 44(2)[6]

☐ Article 45(5)[7]

4.2 Identification of initial grounds of concern

Hazard-based concerns	
Suspected CMR	☐ Carcinogenic ☐ Mutagenic ☒ Reproductive toxicant
Potential ED	☒ Human Health ☒ Environment
Suspected Sensitiser	☐ Respiratory ☐ Skin
Suspected PBT/ vPvB Suspected PMT/ vPvM	☐ Persistent ☐ Bioaccumulative ☐ Mobile ☐ Toxic (as defined in section 4.3 below) ☐ very Persistent ☐ very Bioaccumulative ☐ very Mobile
Other suspected human health hazard(s) (e.g. STOT RE)	☐ (as defined in section 4.3 below)
Other suspected environmental hazard(s)	☐ (as defined in section 4.3 below)
Exposure/ risk-based concerns	
Wide dispersive use	☒
Consumer use	☐
Exposure of workers	☒
Exposure of sensitive populations	☐
Exposure of environment	☒
Cumulative exposure	☐
High RCR	☐
High (aggregated) tonnages	☐
Others (to be specified)	☐

[6] "The Agency shall use the criteria in paragraph 1 […]. Substances shall be included if there are grounds for considering (either on the basis of a dossier evaluation carried out by the Agency or on the basis of any other appropriate source, including information in the registration dossier) that a given substance constitutes a risk to human health or the environment."

[7] "A Member State may notify the Agency at any time of a substance not on the Community rolling action plan, whenever it is in possession of information which suggests that the substance is a priority for evaluation. […]".

4.3 Justification of the concern(s) – to be clarified under Substance evaluation

Existing data supporting the hazard-based concern and other relevant information to justify the inclusion in CoRAP

EC 217-121-1, 227-033-5, 242-895-2 and 248-607-1 all belong to the group of BPA derivatives and possibly share the same hazard profile as BPA which has been identified as a substance of very high concern due to it being toxic for reproduction and an endocrine disruptor for human health and the environment. BPA has a harmonized classification as toxic for reproduction cat. 1B (Repr. 1B; H360F).

In addition to the structural similarities to BPA, several lines of evidence for these substances are suggesting ED properties for ENV and HH and potential for reproductive toxicity.

QSAR:

In the Danish QSAR database, there are positive predictions (in domain) for EC 217-121-1 for estrogen receptor binding and activation. In addition, the prediction is positive (in domain) for androgen receptor inhibition.

Danish QSAR predictions for EC 227-033-5 are positive (in domain) for estrogen receptor binding and activation. The prediction is inconclusive (out of domain) for androgen receptor inhibition.

EC 242-895-2 and 248-607-1 are both predicted to be negative (out of domain) for estrogen receptor binding and negative (in domain) for estrogen receptor activation in the Danish QSAR database. Predictions for androgen receptor inhibition are inconclusive (out of domain). However, for both substances, the OECD QSAR Toolbox v.4.2 profilers predict their metabolites to be strong/very strong estrogen receptor binders.

In vitro:

The estrogenic and anti-estrogenic activity of BPA and BPA-analogues including EC 217-121-1 has been investigated in a carp hepatocyte (CARP-HEP) assay by measuring the effects on the production of vitellogenin (VTG) and CYP1A-mediated catalytic activity in exposed hepatocytes from male carp (Cyprinus carpio). VTG is a precursor of yolk proteins and VTG synthesis is induced by estrogen-dependent stimulation of gene expression. Therefore, VTG is used as a specific biomarker of exposure to (anti)estrogenic compounds. In this study, it was demonstrated that EC 217-121-1 inhibited VTG production and thus has the potential to act as an anti-estrogen *in vitro*. In addition, the substance inhibited aromatase activity (CYP19), which is involved in the conversion of androgens to estrogens in H295R cells (Letcher *et al.*, 2005).

Estrogenic activity has been demonstrated for EC 227-033-5. In an *in vitro* assay investigating the estrogenic activity of BPA and BPA derivatives and the binding energies to human estrogen receptor alpha (hERα), BPA and all of the tested analogues including EC 227-033-5 were found to be estrogenically active. The binding energy of EC 227-033-5 to hERα was in the same order of magnitude as the binding energy of BPA (Zhang *et al.*, 2010). In another *in vitro* study characterizing the estrogenic and androgenic activities of BPA derivatives, EC 227-033-5 was found to induce both estrogen receptor ERα and ERβ-mediated activity (Pelch *et al.*, 2019). Kitamura *et al.* (2005) investigated bisphenol derivatives in a estrogen response element (ERE)-luciferase reporter assay in MCF-7 cells and also found both estrogenic and anti-estrogenic activity for EC 227-033-5. In addition, EC 227-033-5 also showed the highest anti-androgenic activity of all tested bisphenol derivatives.

In vivo:

Combined repeated dose toxicity studies with the reproduction/developmental toxicity screening tests (OECD TG 422) are available for EC 217-121-1 and EC 227-033-5.

For 217-121-1, there were no treatment-related effects on mating performance as assessed by pre-coital interval according to the registrant. However, in the high dose group, the number of matings that resulted in pregnancy was clearly lower than in the control group and the other treated groups. Furthermore, in the high dose group, lower absolute and body weight relative prostate and seminal vesicles weights attained statistical significance when compared to the control group. No effects were observed in testes. There were also significantly reduced pituitary weights in all the dose groups. No relevant effects were observed in offspring.

For EC 227-033-5, no effects on organ weights were observed and no substance-related effects on F0 spermatogenesis endpoints in males were observed according to the registrant.

The exposure duration in these tests may have been too short for manifestation of effects related to endocrine disruption and/or reproductive toxicity. Doses up to 1000 mg/kg/day was used for 227-033-5 while the top dose for 217-121-1 was initially 750 mg/kg/day but reduced to 500 mg/kg/day after one week due to adverse body weight effects for some males at 750 mg/kg/day during the first week of the study. It appears that adequate dose levels were used for EC 227-033-5 while the dose levels for EC 217-121-1 and especially the rationale for the dose reduction should be scrutinized further.

Recently, it is been demonstrated that EC 227-033-5 inhibits the activity of Leydig cell steroidogenic enzymes and induces cell death of Leydig cells in rats, thereby inhibiting the testosterone synthesis in puberty (Hu *et al.*, 2022) as well as in fetal Leydig cells (Li *et al.*, 2022).

Conclusion on the justification for inclusion in the CoRAP

The four substances in this group share similar structures with BPA, which has already been identified as a substance of very high concern based on reproductive toxicity and ED for human health and the environment. Hence, there is a concern for reproductive toxicity and ED for all substances in the group. This is supported by the observed ED-related effects, which are relevant also for reproductive toxicity.

Estrogenic activity has been demonstrated *in silico* for both EC 217-121-1 and EC 227-033-5. In addition, anti-androgenic activity has also been demonstrated *in silico* for EC 217-121-1. *In vitro* data on EC 217-121-1 show that this substance can inhibit VTG production in male carp hepatocytes thus raising a concern for ED ENV. *In vivo* data show that exposure to EC 217-121-1 causes reduced number of matings resulting in pregnancy in rats. Furthermore, lower absolute and relative prostate and seminal vesicles and reduced pituitary weights has been observed in rats raising a concern for reproductive toxicity and for ED HH.

For EC 227-033-5, estrogenic, anti-estrogenic and anti-androgenic activity has been demonstrated *in vitro* and furthermore, inhibition of Leydig cell activity has been demonstrated *in vivo* thus raising a concern for ED HH and indicate a mode of action that may also be relevant for ED ENV. The mechanism behind the observed effects should be subject to further evaluation.

The aggregated tonnages for EC 242-895-2 and 248-607-1 are low and no relevant *in vitro* or *in vivo* studies have been identified in a preliminary literature search. However, *in silico* data and structural similarities to BPA raise concerns for possible ED and for possible regrettable substitution. It is therefore suggested that these substances are also included

in the group for a joint evaluation due to concerns for ED HH and ED ENV. The available information on the substances in the group raise concerns for reproductive toxicity and endocrine disruption for human health and the environment. However, the available information is not sufficient to conclude on the hazards and hence, these substances are proposed for CoRAP inclusion.

Information to be potentially requested

Further information may be needed to clarify the identified concerns for reproductive toxicity and endocrine disruption for human health and the environment. To clarify these concerns and to gain further insights in potential mode(s) of action, a uterotrophic assay (OECD TG 440) could be requested for HH and/or a Fish short-term reproduction assay (OECD TG 229), a 21-day fish assay (OECD TG 230) or a Fish Sexual Development Test (OECD TG 234) could be requested for one or more of the substances to clarify the concern for ED ENV. Higher tier studies with longer exposure duration could also be requested. It is acknowledged that the different modalities ((anti)estrogenic, (anti)androgenic and/or steroidogenic) may be interlinked and therefore, other studies targeted towards other modalities could also be requested. However, the most appropriate testing strategy will be decided in the course of the substance evaluation.

Possible follow-up (demonstrating the improvement of risk management measures)

EC/ List number	Harmonised C&L	SVHC	Restriction	Authorisation	Other
217-121-1	☒	☐	☐	☐	☐
227-033-5	☒	☐	☐	☐	☐
242-895-2	☒	☐	☐	☐	☐
248-607-1	☒	☐	☐	☐	☐

5. References

Hu, D.; Tian, L.; Li, X.; Chen, Y.; Xu, Z.; Ge, R. & Wang, Y. (2022): "Tetramethyl bisphenol a inhibits leydig cell function in late puberty by inducing ferroptosis", *Ecotoxicology and Environmental Safety*, vol. 236 (2022), 113515, doi.org/10.1016/j.ecoenv.2022.113515

Kitamura, S.; Suzuki, T.; Sanoh, S.; Kohta, R.; Jinno, N.; Sugihara, K.; Yoshihara, S.; Fujimoto, N.; Watanabe, H. & Ohta, S. (2005): "Comparative Study of the Endocrine-Disrupting Activity of Bisphenol A and 19 Related Compounds", *Toxicological Sciences*, vol. 84 (2005), pp. 249-259, doi:10.1093/toxsci/kfi074

Letcher, R.; Sanderson, J.; Bokkers, A.; Giesy, J. & Berg, M. (2005): "Effects of bisphenol A-related diphenylalkanes on vitellogenin production in male carp (Cyprinus carpio) hepatocytes and aromatase (CYP19) activity in human H295R adrenocortical carcinoma cells", *Toxicology and Applied Pharmacology*, vol. 209 (2005), pp. 95-104, doi:10.1016/j.taap.2005.03.013

Li, X.; Meng, F.; Ye, L.; Qiao, X.; Li, J.; Tian, L.; Su, M.; Lin, R. & Wang, Y. (2022): "Tetramethyl bisphenol A stimulates proliferation but inhibits fetal Leydig cell function in male rats by targeting estrogen receptor α after in utero exposure", *Environmental Toxicology*, vol 37 (2022), pp. 2743–2755. DOI: 10.1002/tox.23633

Pelch, K.; Li, Y.; Perera, L.; Thayer, K. & Korach, K. (2019): Characterization of Estrogenic and Androgenic Activities for Bisphenol A-like Chemicals (BPs): "In Vitro Estrogen and Androgen Receptors Transcriptional Activation, Gene Regulation, and Binding Profiles", *Toxicological Sciences*, vol. 172(1), 2019, pp. 23-37, doi: 10.1093/toxsci/kfz173

Zhang, H.; Hu, X.; Yin, D. & Lin, Z. (2010): "Development of molecular docking-based binding energy to predict the joint effect of BPA and its analogs", *Human and Experimental Toxicology*, vol. 30(4), pp. 318–327, DOI: 10.1177/0960327110372400