baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	4,4'-isopropylidenedi-o-cresol
EC Number:	201-240-0
CAS Number:	79-97-0
Authority:	Germany
Date:	17/03/2021

Cover Note

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

1 IDENTITY OF THE SUBSTANCE 3

1.1 Other identifiers of the substance 3

1.2 Similar substances/grouping possibilities 3

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION 4

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION) 5

3.1 Classification 5
3.1.1 Harmonised Classification in Annex VI of the CLP 5
3.1.2 Self classification 5
3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP 5

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES 5

4.1 Tonnage and registration status 6

4.2 Overview of uses 7

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CORAP SUBSTANCE 8

5.1. Legal basis for the proposal 8

5.2. Selection criteria met (why the substance qualifies for being in CoRAP) 8

5.3. Initial grounds for concern to be clarified under Substance Evaluation 8

5.4. Preliminary indication of information that may need to be requested to clarify the concern 10

5.5. Potential follow-up and link to risk management 10

1 IDENTITY OF THE SUBSTANCE

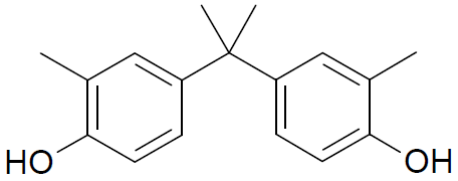
1.1 Other identifiers of the substance

Table: Other Substance identifiers

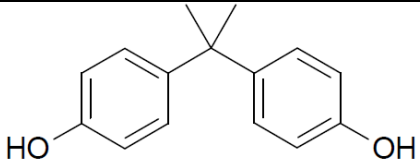
EC name (public):	4,4'-isopropylidenedi-o-cresol
IUPAC name (public):	4-[2-(4-hydroxy-3-methylphenyl)propan-2-yl]-2-methylphenol
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_{17}H_{20}O_2$
Molecular weight or molecular weight range:	256.3395 g/mol
Synonyms:	*Bisphenol C* *BPC* *Bis-C*

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

Structural formula:



1.2 Similar substances/grouping possibilities

Name	EC	structural formula
4,4'-isopropylidenediphenol ("Bisphenol A")	201-245-8	

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	☐ Compliance check
		☒ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restriction	☐ Annex XVII[1]
CLH	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	☐ Dangerous substances Directive 67/548/EEC (NONS)	
	☐ Existing Substances Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment	
	☐ In relevant Annex	
Other processes/ EU legislation	☐ Other (provide further details below)	
Further details	There is one concluded testing proposal evaluation (TPE) and one ongoing TPE on genetic toxicity in vivo.	

[1] Please specify the relevant entry.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no Annex VI entry in CLP available for the substance.

3.1.2 Self classification

- In the registration:

Skin Sens. 1	H317
Eye Irrit. 2	H319
Aquatic Chron. 2	H411

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

Skin Irrit. 2	H315
STOT SE 2	H335
STOT RE 2	H373
Muta. 2	H341

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

There is no CLH proposal available for the substance.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[2]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☒ 10 – 100 tpa	☐ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
There are currently two active registrations for the substance.		

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

[2] Dissemination site accessed on 29 June 2020.

4.2 Overview of uses

Table: Uses

Part 1:

☐ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☐ Consumer use	☒ Article service life	☐ Closed system

Part 2:

	Use(s)
Uses as intermediate	Industrial use as intermediate; Manufacture of other substances
Formulation	Industrial repackaging of Bis-C; Formulation of preparations; Formulation of epoxy resin hardners; Industrial Repackaging of Bis-C
Uses at industrial sites	Use of BPC as laboratory reagent; Industrial use in epoxy adhesives and encapsulants; Manufacture of thermal paper – formulation into materials; Manufacture of epoxy resins, epoxy resin hardeners and polycarbonate; Recycling of thermal paper; Manufacture of coating materials; Industrial use (reactive process regulator); Industry use of BPC for manufacturing polymers
Uses by professional workers	Professional use of BPC as Anti-Oxidant for processing PVC; Professional use of epoxy resin hardeners
Consumer Uses	
Article service life	Professional use of articles made of polycarbonate (outdoor and indoor); Professional use of articles made of epoxy resin (outdoor and indoor); Professional use of articles made of PVC (outdoor and indoor); Service life of thermal paper (Consumer, outdoor and professional worker, outdoor);

In one registration, the following information with regard to uses is included: "This substance is only imported into the EU as a monomer bound in polymer(s) and as polymers are exempt from the REACH registration and the lifecycle of the monomer ends when polymerisation occurs: no identified uses are reported here." According to the disseminated information, no uses are advised against for the substance.

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☐ Article 44(2)

☒ Article 45(5)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☒ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☐ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☐ C ☐ M ☒ R	☒ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[3]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☐ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☐ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[3] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

Reproduction toxicity

In a screening study in rats (OECD TG 421, 2019) where BPC was administered orally, a lower fertility index and lower number of implantation sites were reported at the mid and highest dose. However, the biological relevance of these results cannot be confirmed, because the changes in the number of implantation sites are poorly reported (no control and lowest dose values) and the available values do not show a dose response increase. In addition, they are reported to be "almost same values as historical control data at the test facility".

Endocrine disrupting properties

In a 28-d study on the substance in rats, increased absolute and relative adrenal glands weight, increased absolute ovaries weight, increased relative brain weight were observed at the lowed dose level (40 mg/kg bw/day) in addition to a statistically significant decrease in total cholesterol levels (by 33%) in male rats at the highest dose group.

Several in vitro studies indicate estrogenic and antiandrogenic properties for BPC (e.g. Kitamura et al. 2005; Pelch et al. 2017; Wang et al. 2014). Due to the structural similarity of BPC to BPA (an identified ED) and its substitute BPS, a potential for endocrine disrupting properties is also conceivable for this substance. This concern should be further investigated.

Regarding the environment no studies are available that allow a conclusion on the ED properties of this substance. Taking together the structural similarity of BPCto BPA and the human health data, there is also a concern that BPCcan act as an ED in the environment. This concern can be clarified during the proposed substance evaluation.

Uses and exposure

The substance is structurally similar to and registered for similar uses as Bisphenol A (polycarbonate, epoxy resin, thermal paper). As Bisphenol A is restricted for use in thermal paper since 2020, a shift towards the use of Bisphenol C as a "drop-in" alternative is possible.

References

Pelch, Katherine E., et al. "NTP Research Report on Biological Activity of Bisphenol A (BPA) Structural Analogues and Functional Alternatives: Research Report 4." (2017).

Kitamura, Shigeyuki, et al. "Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds." Toxicological Sciences 84.2 (2005): 249-259.

Wang, Si et al. "Extending an in vitro panel for estrogenicity testing: the added value of bioassays for measuring antiandrogenic activities and effects on steroidogenesis." Toxicological sciences : an official journal of the Society of Toxicology vol. 141,1 (2014): 78-89. doi:10.1093/toxsci/kfu103

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☒ Information ED potential	☐ Other (provide further details below)

At the current state of knowledge, it has to be checked whether further studies on the effects of BPC on reproduction and endocrine disruption are necessary and have to be requested from the registrant(s). The submitted data for the endpoint reproductive toxicity is not considered sufficient for a definite assessment of these endpoints.
A possible read-across to BPA will be evaluated more deeply for these endpoints, however, a preliminary check indicated that read-across might not be appropriate.

For mutagenicity, further steps will be considered as soon as the proposed *in vivo* study will become available. accordingly.

5.5. Potential follow-up and link to risk management

☐ Harmonised C&L	☐ Restriction	☐ Authorisation	☒ Other (provide further details)

If this substance has been shown to have an adverse effect on reproduction, a CLH procedure should be initiated with the aim of classifying BPC as Repr. 2, H361f or Repr. 1B, H360F. In addition, in case BPC is considered to be an endocrine disruptor for human health and/or the environment, it could potentially be identified as SVHC according to Article 57f as a potential follow-up measure in case it fulfils the required equivalent level of concern.

If the hazardous properties of the substance are confirmed during the substance evaluation, it is anticipated that a Regulatory Management Option Analysis (RMOA) will be prepared by the evaluating member state to decide on the necessity of further risk management measures.