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):	(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one
EC Number:	253-242-6
CAS Number:	36861-47-9
Authority:	Germany
Date:	18/03/2020

Cover Note

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

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1 IDENTITY OF THE SUBSTANCE

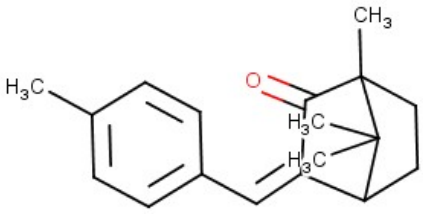
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one
CAS number:	36861-47-9
EC number:	253-242-6
IUPAC name (public):	(3E)-1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]-2-norbornanone
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_{18}H_{22}O$
Molecular weight or molecular weight range:	254.367 g/mol
Synonyms:	*4-MBC* *Neo Heliopan MBC* *Enzacamene*

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

Structural formula:



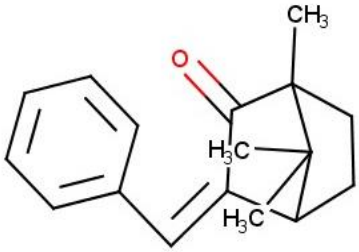
1.2 Similar substances/grouping possibilities

Table: Substance identifiers for structurally similar substance 3-BC

EC name (public):	1,7,7-trimethyl-3-(phenylmethylene)bicyclo[2.2.1]heptan-2-one
EC numer:	239-139-9
CAS number:	15087-24-8
IUPAC name (public):	(3Z)-1,7,7-trimethyl-3-(phenylmethylidene)bicyclo[2.2.1]heptan-2-one
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_{17}H_{20}O$
Molecular weight or molecular weight range:	240.340 g/mol
Synonyms:	*3-BC* *Benzylidene camphor*

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

Structural formula:



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	A Risk Management Option Analysis has been prepared by the DE CA in 2014 and a conclusion has been published in July 2015.[2] An Annex XV dossier for SVHC identification according to Art. 57f) has been prepared by the DE CA following the RMOA conclusion which was submitted for public consultation in 2016.[3] Following	

[1] Please specify the relevant entry.

[2] https://echa.europa.eu/de/rmoa/-/dislist/details/0b0236e1809b80f7

[3] https://echa.europa.eu/de/registry-of-svhc-intentions/-/dislist/details/0b0236e180e47ae7

	discussion of the dossier at the 48. Meeting of the Member State Committee, the dossier was withdrawn by the submitting CA. 4-MBC is included on Annex VI of Regulation (EC) No 1223/2009 on cosmetic products: Entry 18 of Annex VI specifies that 4-MBC may be used as a UV filter in a concentration up to 4% in ready for use preparations. In May 2019, the European Commission has initiated a call for data for 4-MBC alongside 13 other cosmetic ingredients with potential endocrine-disrupting properties with regard to human health.[4]

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

3.1.2 Currently, there is no entry in Annex VI of CLP Regulation (Regulation (EC) 1272/2008) for 4-MBC. Self classification

- In the registration:

Self classification

Name	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
			Hazard Class and Category Code(s)	Hazard statement code(s)		
(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one	253-242-6	36861-47-9	STOT RE 2 (Thyroid)	H373		

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

[4] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products_en

Additional notified hazard classes

Name	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
			Hazard Class and Category Code(s)	Hazard statement code(s)		
(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one	253-242-6	36861-47-9	Skin Irrit. 2 Eye Irrit. 2 Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H315 H319 H361 H400 H410		

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

No proposal for harmonised classification and labelling for 4-MBC has been submitted.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[5]

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

*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

[5] *ECHA dissemination site accessed on 15 July 2019.*

4.2 Overview of uses

The following uses have been registered under REACH

Table: Uses

Part 1:

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

The substance is used as a UV filter in cosmetics and personal care products.

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[6]	
☐ 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)
Available *in silico*, *in vitro* and *in vivo* data as well as the evidence from the structurally similar camphor substance 1,7,7-trimethyl-3-(phenylmethylene)bicyclo[2.2.1]heptan-2-one (3-BC), which is already identified as SVHC based on its endocrine disrupting effects in the environment, provide strong grounds for the suspicion that 4-methylbenzylidene camphor (4-MBC) acts via endocrine modes of action and that this endocrine activity can lead to adverse effects in environmental species like fish and amphibians.		

Available in vitro tests (Schlumpf et al. (2004a), Heneweer et al. (2005), Matsumoto et al. (2005), Schlumpf et al. (2001), Jimenez-Diaz et al. (2013), Schmitt et al. (2008), Gomez et al. (2005), Schreurs et al. (2005), Schreurs and van der Burg (2002), Kunz and Fent (2006), Ma et al. (2003), Schiffer et al. (2014), Hofmann et al. (2009)) show positive and dose dependent estrogenic results i.e. activation of the receptors or cell proliferation due to the activation of ER systems after incubation with 4-MBC. One proliferation study using MCF-7 cells could furthermore demonstrate that the observed proliferative effect of 4-MBC was ER mediated. There are contradicting results for the antiandrogenic activity of 4-MBC with two studies showing a clear antiandrogenic effect and one study showing no effect up to the highest tested concentration of 10 µM of 4-MBC. Two studies investigated the progesterone-like acitivity of 4-MBC. In summary, 4-MBC shows antagonistic acitivity, which could be reversed by coincubation with a stable PR agonist. Similar to progesterone 4-MBC activates the calcium channels on sperm cells (CatSper) which affects their swimming behaviour. Additionally, one study showed the potential of 4-MBC to interact with thyroidal pathways. Transfected cells showed an increase in T3 reporter gene transcription after a 8 h incubation with 4-MBC. The same study found that 4-MBC acted antagonistically in a thyroid receptor binding assay compared to the natural ligand T3. Thus, on an in vitro level there is evidence for a possible multi pathway endocrine activity of 4-MBC.

In fish, 4-MBC induces estrogen-responsive gene products including vitellogenin (Inui et al. (2003)). Kunz et al. (2006) found no estrogenic activity of 4-MBC in a test with junvenile fish. In mammalians, equivocal estrogenic activity and effects on endocrine sensitive endpoints in developmental studies were found. The uterotrophic assays by Schlumpf et al. (2004) and Tinwell et al. (2002) demonstrated estrogenic effects, whereas Ashby et al. (2004) could not confirm these results. Additionally, an increase in uterine weight has been observed in a three month study performed by Seidlova-Wuttke et al. (2006) combined with histopathological markers in uterus and vagina pointing to an endocrine mode of action. Perinatal studies showed alterations in reproductive organ weight at birth, on day 14 and in adulthood, delayed sexual maturation, and altered gene expression in prostate and brain in male rats, while effects observed in females included increased uterus weights, changes in gene expression of estrogen regulated genes in brain and uterus, as well as strongly impaired sexual behaviour such as reduced proceptive and lordosis behaviour and increased rejection behaviour. Furthermore, some studies indicated thyroid mediated effects in mammals including increased TSH levels and decreased T4 levels as well as increased thyroid gland weights.

[6] 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

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)

As described above, the available data for 4-MBC point to an endocrine activity mainly via the HPG and HPT axis. To clarify the concern that this observed endocrine activity of 4-MBC leads to adverse effects in environmental species the following assays might be potentially requested:

- Fish sexual development test according to OECD TG 234
- Amphibian metamorphosis assay according to OECD TG 231

5.5. Potential follow-up and link to risk management

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

If, based on the outcome of the substance evaluation, 4-MBC is found to meet the criteria of an endocrine disruptor for the environment the need for further risk management measures under REACH like SVHC identification according to art. 57(f) or a restriction will be assessed by the eMSCA.

References

Gomez, E., Pillon, A., Fenet, H., Rosain, D., Duchesne, M.J., Nicolas, J.C., Balaguer, P., Casellas, C., 2005. Estrogenic activity of cosmetic components in reporter cell lines: Parabens, UV screens, and musks. Journal of Toxicology and Environmental Health - Part A 68, 239-251.

Heneweer, M., Muusse, M., van den Berg, M., Sanderson, J.T., 2005. Additive estrogenic effects of mixtures of frequently used UV filters on pS2-gene transcription in MCF-7 cells. Toxicology and applied pharmacology 208, 170-177.

Inui, M., Adachi, T., Takenaka, S., Inui, H., Nakazawa, M., Ueda, M., Watanabe, H., Mori, C., Iguchi, T., Miyatake, K., 2003. Effect of UV screens and preservatives on vitellogenin and choriogenin production in male medaka (Oryzias latipes). Toxicology 194, 43-50.

Jimenez-Diaz, I., Molina-Molina, J.M., Zafra-Gomez, A., Ballesteros, O., Navalon, A., Real, M., Saenz, J.M., Fernandez, M.F., Olea, N., 2013. Simultaneous determination of the UV-filters benzyl salicylate, phenyl salicylate, octyl salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3-benzylidene camphor in human placental tissue by LC-MS/MS. Assessment of their in vitro endocrine activity. Journal of chromatography. B, Analytical technologies in the biomedical and life sciences 936, 80-87.

Kunz, P.Y., Fent, K., 2006. Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. Aquatic Toxicology 79, 305-324.

Kunz, P.Y., Galicia, H.F., Fent, K., 2006a. Comparison of in vitro and in vivo estrogenic activity of UV filters in fish. Toxicological Sciences 90, 349-361.

Kunz, P.Y., Galicia, H.F., Fent, K., 2004. Assessment of hormonal activity of UV filters in tadpoles of frog Xenopus laevis at environmental concentrations. Marine Environmental Research 58, 431-435.

Ma, R., Cotton, B., Lichtensteiger, W., Schlumpf, M., 2003. UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. Toxicological sciences : an official journal of the Society of Toxicology 74, 43-50.

Matsumoto, H., Adachi, S., Suzuki, Y., 2005. [Estrogenic activity of ultraviolet absorbers and the related compounds]. Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan 125, 643-652.

Schiffer, C., Muller, A., Egeberg, D.L., Alvarez, L., Brenker, C., Rehfeld, A., Frederiksen, H., Waschle, B., Kaupp, U.B., Balbach, M., Wachten, D., Skakkebaek, N.E., Almstrup, K., Strunker, T., 2014. Direct action of endocrine disrupting chemicals on human sperm. EMBO reports 15, 758-765.

Schlumpf, M., Cotton, B., Conscience, M., Haller, V., Steinmann, B., Lichtensteiger, W., 2001. In vitro and in vivo estrogenicity of UV screens. Environmental health perspectives 109, 239-244.

Schlumpf, M., Durrer, S., Faass, O., Ehnes, C., Fuetsch, M., Gaille, C., Henseler, M., Hofkamp, L., Maerkel, K., Reolon, S., Timms, B., Tresguerres, J.A., Lichtensteiger, W., 2008a. Developmental toxicity of UV filters and environmental exposure: a review. International journal of andrology 31, 144-151.

Schlumpf, M., Jarry, H., Wuttke, W., Ma, R., Lichtensteiger, W., 2004a. Estrogenic activity and estrogen receptor beta binding of the UV filter 3-benzylidene camphor. Comparison with 4-methylbenzylidene camphor. Toxicology 199, 109-120.

Schlumpf, M., Kypke, K., Vökt, C.C., Birchler, M., Durrer, S., Faass, O., Ehnes, C., Fuetsch, M., Gaille, C., Henseler, M., Hofkamp, L., Maerkel, K., Reolon, S., Zenker, A., Timms, B., Tresguerres, J.A.F., Lichtensteiger, W., 2008b. Endocrine active UV filters: Developmental toxicity and exposure through breast milk. Chimia 62, 345-351.

Schlumpf, M., Schmid, P., Durrer, S., Conscience, M., Maerkel, K., Henseler, M., Gruetter, M., Herzog, I., Reolon, S., Ceccatelli, R., Faass, O., Stutz, E., Jarry, H., Wuttke, W., Lichtensteiger, W., 2004b. Endocrine activity and developmental toxicity of cosmetic UV filters--an update. Toxicology 205, 113-122.

Schreurs, R.H.M.M., Sonneveld, E., Jansen, J.H.J., Seinen, W., van der Burg, B., 2005. Interaction of Polycyclic Musks and UV Filters with the Estrogen Receptor (ER), Androgen Receptor (AR), and Progesterone Receptor (PR) in Reporter Gene Bioassays. Toxicological science 83, 264-272.

Schreurs, R.L., Peter; Seinen Willem;, van der Burg, B., 2002. Estrogenic activity of UV filters determined by an in vitroreporter gene assay and an in vivo transgenic zebrafish assay. Arch Toxicol 2002, 257–261.

Seidlova-Wuttke, D., Christoffel, J., Rimoldi, G., Jarry, H., Wuttke, W., 2006. Comparison of effects of estradiol with those of octylmethoxycinnamate and 4-methylbenzylidene camphor on fat tissue, lipids and pituitary hormones. Toxicology and applied pharmacology 214, 1-7.

Seidlova-Wuttke,D., Jarry,H., Christoffel,J., Rimoldi,G., and Wuttke,W., 2006. Comparison of effects of estradiol (E2) with those of octylmethoxycinnamate (OMC) and 4-methylbenzylidene camphor (4MBC) – 2 filters of UV light - on several uterine, vaginal and bone parameters. Toxicology and Applied Pharmacology 210, 246-254.

Tinwell, H., Lefevre, P.A., Moffat, G.J., Burns, A., Odum, J., Spurway, T.D., Orphanides, G., Ashby, J., 2002. Confirmation of uterotrophic activity of 3-(4-methylbenzylidine)camphor in the immature rat. Environ Health Perspect 110, 533-536.

Tsui, M.M., Leung, H.W., Lam, P.K., Murphy, M.B. 2014. Seasonal occurrence, removal efficiencies and preliminary risk assessment of multiple classes of organic UV filters in wastewater treatment plants. Water Res 53, 58-67.