Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran (HHCB)
EC Number:	214-946-9
CAS Number:	1222-05-5
Authority:	France
Date:	22/03/2022

Cover Note

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

1 IDENTITY OF THE SUBSTANCE

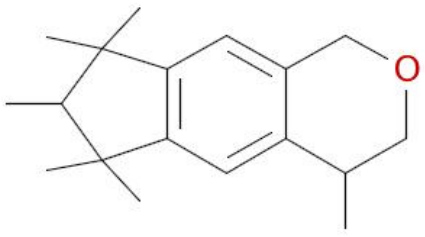
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	HHCB
IUPAC name (public):	4,6,6,7,8,8-hexamethyl-1,3,4,6,7,8-hexahydrocyclopenta[g]isochromene
Index number in Annex VI of the CLP Regulation:	603-212-00-7
Molecular formula:	C18H26O
Molecular weight or molecular weight range:	258.3984
Synonyms:	*Cyclopenta(g)-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-* 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran *Galaxolide*

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

Structural formula:



1.2 Similar substances/grouping possibilities

Not relevant

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
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 assessment report of the substance HHCB has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances (Final version, May 2008). It has been concluded that there is no need for risk reduction measures beyond those which are being applied already (conclusion (ii)) both for the Environment and human health. Furthermore, in the RAR published in 2008, the Netherlands concluded that HHCB does not meet the criteria for PBT substances. This point is currently under discussion based on new methods and data available which allow a re-assessment of the PBT properties of this substance.	

	In addition, following a compliance check (CCH) a decision has been adopted on the 31st of October 2018. A pre-natal developmental toxicity study (OECD TG 414) and an extended one-generation reproductive toxicity study (OECD TG 443), with additional cohorts 1A and 1B (with extension to mate the Cohort 1B animals to produce the F2 generation) were submitted in June 2021 in response to the CCH. Regarding other regulatory framework, HHCB has been evaluated by the SCCNFP (Scientific Committee on Cosmetic products and Non-Food Products intended for consumers) for its use as fragrance ingredient in cosmetic products (SCCNFP/0610/02, final report, 17 September 2002). SCCNFP considers that HHCB can be safely used in cosmetics without any restriction for its use. Other sources of consumer exposure from non food products (e.g. laundry products) have not been considered.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

Table: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
603-212-00-7	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran galaxolide (HHCB)	214-946-9	1222-05-5	Aquatic Acute 1 Aquatic Chronic 1	H400 H410		

3.1.2 Self classification

- In the registration dossiers: harmonised classification without further addition
- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:
    - Skin Irrit 2 – H315
    - Repr 2 – H361

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

None

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[1]

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
Please provide further details if appropriate (e.g. if more than one submission, joint/individual).		

***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

4.2 Overview of uses

The substance is used in the following products: biocides (e.g. disinfectants, pest control products), washing & cleaning products, air care products, polishes and waxes, perfumes and fragrances and cosmetics and personal care products.

HHCB is the largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which HHCB is mixed. Applications of the fragrance oils are in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products, air fresheners etc. (EU RAR, 2008).

[1] *Dissemination site accessed on 20 October 2021.*

Table: Uses

Part 1:

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

Part 2:

	Use(s)
Uses as intermediate	
Formulation	Formulation of dertergents and maintenance products Formulation of fragrance products (cosmetics)
Uses at industrial sites	Industrial use of washing and cleaning products Industrial use of dertergents and maintenance products
Uses by professional workers	Polishes and wax blends Detergents and maintenance products
Consumer Uses	Cosmetics, air care products, washing and cleaning products, biocides
Article service life	

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[2]	
☐ 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)
Endocrine disruption: Data on endocrine properties of HHCB in vertebrates are limited to some *in vitro* and *in vivo* mechanistic studies (OECD level 2 and 3).		

[2] 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

An endocrine activity has been observed on ER pathway. Several *in vitro* studies report a weak agonist activity on ERα and an antagonist activity on ERβ. In short-term exposure tests performed on fish, HHCB induced the VTG mRNA expression in adult male medaka, indicating an estrogenic effect. In contrast, only anti-estrogenic activity of HHCB was observed in juvenile ERE-luciferase transgenic zebrafish exposed for 96 h. The *in vivo* results support these *in vitro* findings and highlight the differential capacity of HHCB to interfere with ER signalling. Albeit an alert on ER signalling could be identified, information on HHCB effects on reproduction and development of the fish would be needed to draw a firm conclusion about the HHCB (anti)estrogenic effects.

Regarding other signaling pathways, the available data are not sufficient to conclude. There is no sufficient information on AR signaling pathway. In addition, an alert on steroidogenic activity has been identified, but information needs to be requested to confirm the observed effect.

Regarding the vertebrate toxicity related to human and environmental health, there is a lack of information on reproductive and developmental toxicity. Based on the only *in vivo* test measuring only one endpoint (Seinen et al., 1999), it is not possible to conclude whether or not HHCB displays endocrine adverse effects.

Contrasting with vertebrates, the reproductive toxicity of HHCB on invertebrates has been evidenced in several studies. These studies highlight the possible ED properties of HHCB in arthropods, worms and molluscs. However, based on current knowledge, no biological plausible link can be established between a reproductive adverse effect in invertebrates and an endocrine mode of action, as this is required for the identification of an ED based on the EU definition and criteria (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009).

In this context, further investigations are needed, particularly on long-term reproductive and developmental toxicity in vertebrates (rodent and/or fish) and on endocrine mechanisms in invertebrate species, to assess the ED properties of HHCB.

A pre-natal developmental toxicity study (OECD TG 414) and an extended one-generation reproductive toxicity study (OECD TG 443), with cohorts 1A and 1B (with extension to mate the Cohort 1B animals to produce the F2 generation) have been submitted in June 2021 in the context of a compliance check (CCH). These studies may provide useful information to state on the ED long-term effects for human health. After evaluating the new dataset, other studies could be considered. Further work on environmental health within substance evaluation would be necessary to clarify the concern on endocrine effects in fish.

PBT properties: Regarding PBT properties, the substance has been assessed by Netherlands under the previous legistation. The EU-RAR (2008) associated with this assessment concluded that HHCB is not PBT. However, there is a need to reassess the PBT properties of the substance based on the new methods and new data available. Discussions in the PBT EG are currently ongoing. Further information, if needed, could be requested in the context of substance evaluation.

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)
Additional studies to elucidate endocrine disruptive properties and/or PBT properties of HHCB may be requested.	

5.5. Potential follow-up and link to risk management

☐ Harmonised C&L	☐ Restriction	☒ Authorisation	☐ Other (provide further details)
PBT and ED properties, if confirmed, can trigger an SVHC identification.			