Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	Ethyl 4-hydroxybenzoate
EC Number:	204-399-4
CAS Number:	120-47-8
Authority:	Germany
Date:	21/03/2017

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

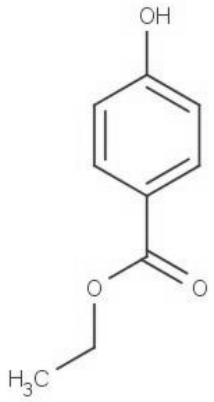
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	Ethyl 4-hydroxybenzoate
IUPAC name (public):	ethyl 4-hydroxybenzoate
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	$C_9H_{10}O_3$
Molecular weight or molecular weight range:	166.17 g/mol
Synonyms:	Benzoic acid, 4-hydroxy-, ethyl ester ETHYL PARABEN Ethylparaben Faracide E Microcare EHB Paratexin E Solbrol A

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, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restric -tion	☐ Annex XVII
Harmonised C&L		☐ 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 Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation 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		Regulated in cosmetic products as described in Annex V of the Regulation (EC) No 1223/2009 on Cosmetic Products. Included in Annex II (list of permitted food additives) of the Regulation (EC) No 1333/2008 on Food Additives.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no harmonised Classification for the substance in Annex VI.

3.1.2 Self classification

- In the registration:

  Not classified

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

Asp. Tox. 1	H304	
Skin Irrit. 2	H315	
Skin Sens. 1	H317	
Eye Irrit. 2	H319	
STOT SE 3	H335	(respiratory system)
Acute Tox. 4	H302	
Resp. Sens. 1	H334	

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

No Proposal for Harmonised Classification and Labeling has been submitted to the Registry of Intentions.

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
Joint submission.		

4.2 Overview of uses

Ethyl 4-hydroxybenzoate like other parabens has a widespread use as preservatives in foods, pharmaceuticals, and cosmetics.

Table: Uses

Part 1:

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

[1] *The dissemination site was accessed 20 September 2016.*

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

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)

[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

Various *in vitro* studies using human cell lines reported that ethyl 4-hydroxybenzoate, similarly to other parabens, can elicit weak estrogenic responses (Blair et al. 2000; Byford et al. 2002; Gomez et al. 2005; Kim et al. 2011, and Yang et al. 2012).

An *in vivo* fish study using sexually immature rainbow trout confirmed that ethyl 4-hydroxybenzoate, similarly to other parabens, could evoke estrogenic response: after repeated injections with ethyl 4-hydroxybenzoate, significant vitellogenin induction could be measured in the highest dose tested (Pedersen et al., 2000).

In vivo rat studies were, however, contradictory: Vo et al. (2010) measured significant weight changes in ovaries, adrenal glands, thyroid glands, liver, as well as kidneys and observed histopathological alterations in reproductive organs. Furthermore, the authors measured a significant decrease in serum estradiol and thyroxin concentrations. Similarly, Lemini et al. (2004) presented evidence of estrogenicity using a morphometric analysis of uteri from mice treated with ethyl 4-hydroxybenzoate. In contrast, it was shown by Oishi (2004) that ethyl 4-hydroxybenzoate does not adversely affect the secretion of sexual hormones or the male reproductive function in rats. Similarly, using the ovariectomized mouse uterotrophic bioassay, ethyl 4-hydroxybenzoate was negative for both estrogen agonistic and antagonistic effects (Ohta et al., 2012).

Besides estrogenic effects, interaction with steroidogenesis using the adrenal H295R steroidogenesis assay was detected causing a significant increase in the progesterone formation (Taxvig et al., 2008). Furthermore, glucocorticoid activity for ethyl 4-hydroxybenzoate was identified in vitro using the human breast carcinoma MDA-kb2 cell line which expresses both the androgen and the glucocorticoid-responsive reporter (Kolsek et al., 2015).

As available data on the uses of the substance suggest that there is relevant exposure of the environment to the substance, further tests may be required to clarify the concern of endocrine disruption to the environment.

It is to be noted, that substance evaluations are running under the scope of endocrine disruption for two similar substances (EC 202-307-7 propyl paraben by Belgium 2015 and EC 202-785-7 methyl paraben by France 2014). Outcomes from these substance evaluations might influence that of ethyl 4-hydroxybenzoate. Therefore, ethyl 4-hydroxybenzoate should be included in the 3rd CoRAP year for the CoRAP update 2017/2019.

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)

Based on the preliminary evaluation of the data related to endocrine disrupting properties of ethyl 4-hydroxybenzoate, chronic studies using aquatic vertebrate could be requested to clarify the concern on the estrogenic effects in the environment. Additionally, a detailed evaluation of the available data may lead to further information requirements.

5.5. Potential follow-up and link to risk management

☐ Harmonised C&L	☒ Restriction	☒ Authorisation	☐ Other (provide further details)
Depending on the outcome of the substance evaluation, an analysis of Risk Management Options shall be carried out to identify appropriate risk management measures.			

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