Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	2,6-di-tert-butyl-p-cresol
EC Number:	204-881-4
CAS Number:	128-37-0
Authority:	French MSCA
Date:	22/03/2016

Note

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

Contents

1 IDENTITY OF THE SUBSTANCE

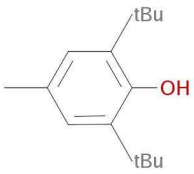
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	2,6-di-tert-butyl-p-cresol
IUPAC name (public):	2,6-di-tert-butyl-4-methylphenol
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$C_{15}H_{24}O$
Molecular weight or molecular weight range:	220.35
Synonyms:	butylated hydroxytoluene 2,6-di-*tert*-butyl-4-methylphenol, 2,6-di-*tert*-butyl-*p*-cresol (DBPC), 3,5-di-*tert*-butyl-4-hydroxytoluene

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

Structural formula:



1.2 Similar substances/grouping possibilities

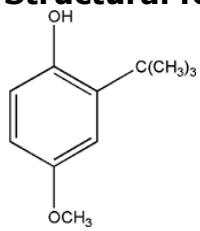
BHT and BHA (buytlated hydroxyanisole) are closely related butylated compounds used as synthetic antioxidants. The uses, as well as the concerns, relating to these two substances also seem to be very similar.

EC name:	246-563-8
IUPAC name:	tert-butyl-4-methoxyphenol
Index number in Annex VI of the CLP Regulation	none
Molecular formula:	$C_{11}H_{16}O_2$
Molecular weight or molecular weight range:	180,2 g/mol
Synonyms/Trade names:	tert-butyl-hydroxyanisole; Butylated hydroxyanisole (BHA)

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

BHA consists of a mixture of two isomers: 3-tert-butyl-4-hydroxyanisole (3-BHA) and 2-tert-butyl-4-hydroxyanisole (2-BHA). The purity is specified to be not less than 98.5% of $C_{11}H_{16}O_2$ and not less than 85% of the 3-BHA. Therefore BHA can be considered as a monoconstituent substance.

Structural formula:



Structural formula: *(If it is group of similar substance, give examples)*

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	

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)		
No current							

3.1.2 Self classification

- In the registration dossier:

In its registration dossier, the lead registrant classifies BHT as Aquatic Chronic of category 1 (H410) and Aquatic Acute Category 1 (H400).

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

Hazard Class and Category Code(s)	Hazard Statement Code(s)
Acute Tox. 4	H302
Acute Tox. 4	H312 (dermal)
Acute Tox. 4	H332 (inhalation)
Acute Tox 3	H310
Skin Irrit. 2	H315
Eye Irrit. 2	H319
Skin Sens. 1	H317
Resp. Sens 1	H334
STOT SE 3	H335
Muta. 1B	H340

Muta.2	H341
Carc. 2	H351
Carc. 1B	H350
Repr. 2	H361
STOT SE 1	H370 (nervous system)
STOT RE2	H373 (lung, liver)
STOT RE2	H373 (liver)
Aquatic Acute 1	H400
Aquatic Chronic 2	H411
Aquatic Chronic 1	H410
Aquatic Chronic 4	H413

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

There is no current proposal for classification nor any intention indicated in the Registry of intentions.

The data presented here below might warrant discussion at the RAC level respectively for carcinogenic and reprotoxic effects of BHT, at least for having identical classification & labelling proposed. Indeed, given the heterogenicity of the self classifications, proposing an harmonized classification as a risk management option will be envisaged.

Hazards properties are mainly based on previous National and European evaluations cited below:

- Lanigan *et al* 2002. Final report on the safety assessment of BHT. *International Journal of Toxicology,* 21(Suppl. 2):19–94, 2002.
- OECD , *2,6-di-tert-butyl-p-cresol (BHT) (CAS No : 128-37-0).* OECD Screening Information Data Sets (SIDS). Orlando (Floride) : UNEP Publication. (2002).
- BUA (GDCh-Advisory Committee on Existing Chemicals) *(*2000*) BUA Report* 219*, Supplementary Report* VI*, S. Hirzel Verlag,* Stuttgart.
- Williams GM*,* Iatropoulos MJ*,* Whysner J *(*1999*).* Safety assessment of butylated hydroxyanisole and butylated hydroxytoluene as antioxidant food additives*. Food Chem Toxicol* **37***:* 1027–1038.
- WHO (JECFA), 1996. 833. Butylated hydroxytoluene. Toxicological evaluation of certain food additives and contaminants in food. Prepared by the forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Safety evaluation of certain food additives. WHO Food Additives Series 35*, World Health Organization,* Geneva, Switzerland. http://www.inchem.org/documents/jecfa/jecmono/v35je02.htm.

BHT has recently been evaluated by the EFSA panel in relation to the use as a food additive and nutrient sources added to food (ANS):

- EFSA Scientific Opinion on the re-evaluation of butylated hydroxytoluene BHT (E 321) as a food additive. EFSA Journal 2012;10(3):2588[43 pp.]. doi:10.2903/j.efsa.2012.2588 http://www.efsa.europa.eu/fr/efsajournal/pub/2588.htm

EFSA has not concluded on BHT's hazardous property regarding its potential endocrine disrupting effect, nor its potential reprotoxic effect but has stated on the risk related to its use as a food additive.

Skin sensitization

On the basis of the animal and clinical data included in this report, the (CIR) Cosmetic Ingredient Review Expert Panel concludes that BHT is safe as used in cosmetic formulations (CIR expert panel, «Final report on the safety assessment of BHT.» *International Journal of Toxicology.* Vol. 21, no. suppl. 2, p. 19-94. (2002)).

As far as regulatory concern, the use of BHA and BHT in cosmetics is not regulated in Canada, although Health Canada has attributed to the BHA a "high health priority" based on its carcinogenic potential, and BHT "moderate health priority". Both chemicals were selected for future assessments under the Management Plan Chemicals government.
International regulations are stricter. The European Union banned the use of BHA as an ingredient in recipes fragrances. The State of California requires warning labels on products for consumers containing BHA, indicating that this ingredient can cause cancer.

Several international and European assessments have been carried out on toxicological effects for carcinogenicity potential and endocrine disruptor potential of BHT in comparison to the similar structure of its analogue BHA.

Carcinogenicity

- *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans vol. 17* (Paris : Centre international de Recherche sur le Cancer), vol. 40 (1986). classified BHA as potentially carcinogen for human.

- *WHO (JECFA) 1996*. 833. Butylated hydroxytoluene. Toxicological evaluation of certain food additives and contaminants in food. Prepared by the forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Safety evaluation of certain food additives. WHO Food Additives Series 35*, World Health Organization,* Geneva, Switzerland.

- *EFSA 2012.* Scientific Opinion on the re-evaluation of butylated hydroxytoluene BHT (E 321) as a food additive. EFSA Journal 2012;10(3):2588[43 pp.].

Endocrine disruptor and reprotoxic effects

- *Study on Enhancing the Endocrine Disrupter Priority List with a Focus on Low Production Volume Chemicals*, Revised Report to DG Environment (Hersholm, Danemark : DHI Water and Environment, 2007), http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf.The european commission on endocrine disruptor listed BHA as a priority substance Cat 1 based on the fact of interfering with hormonal function.

- PNUE and OCDE, *2,6-di-tert-butyl-p-cresol (BHT) Screening Information Data Set: Initial Assessment Report* (Paris: PNUE, 2002), http://www.inchem.org/documents/sids/sids/128370.pdf. A long-term exposure to high doses of BHT is toxic to mice and rats, causing problems to thyroid and other organs (the liver, the kidney, the lungs and the blood)

- TEDX list of potential Endocrine Disruptor : Hughes *et al* 2000. Estrogenic alkylphenols induce cell death by inhibiting testis endoplasmic reticulum Ca(2+) pumps, *Biochem Biophys Res Commun*. 2000 Nov 2;277(3):568-74.

- Some limited data suggest that high doses of BHT can simulate estrogen (Wada, H. *et al*., 2004[1]), sexual primary female hormone, as well as preventing the expression of male sex hormones, which would result in adverse effects on reproduction (Schrader, TJ et GM Cooke, 2000[2]).

3.1.4 CLP Notification Status

There are 89 aggregated notifications by the 25 August 2015 containing a total of 4188 notifications.

Table: CLP Notifications

	CLP Notifications[3]
Number of aggregated notifications	89
Total number of notifiers	4188

[1] Wada, H. *et al*., 2004. «In vitro estrogenicity of resin composites», *Journal of Dental Research* 83, no. 3 (March 2004) : 222-6.
[2] Schrader, TJ et GM Cooke, 2000. «Examination of selected food additives and organochlorine food contaminants for androgenic activity in vitro», *Toxicological Sciences* 53, no. 2 (February 2000) : 278-88.
[3] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 25 August 2015)

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES

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
One individual notifier declares 10000 tonnes per year		

4.2 Overview of uses

Butylated hydroxytoluene (BHT) is at room temperature (20°C) a white, crystalline, odorless solid (IARC 1986). Food grade should contain not less than 99% BHT. It is insoluble in water but soluble in fats. It is also soluble in ethanol. Physical and chemical properties of BHT are listed in the following table.

Property	**Information**
Molecular weight	180.2a
Melting point	69.8°C at 101.3 kPa
Boiling point	266°C at 101.3 kPa
Flash point	127°C at 1013 hPa
Log *K*ow	6.2 mg/L at 20°C
Water solubility	Water solubility = 1.01-1.04 mg/L Soluble in organic solvents
Vapor pressure	0.16 hPa at 50°C

Non flammable, No explosive, No oxidising (solid)

According to OECD, BHT is used as an antioxidant which finds many applications in a wide variety of industries. It is used in ground vehicle and aviation gasolines; lubricating, turbine, and insulation oils; waxes, synthetic and natural rubbers, paints, plastics, and elastomers. It protects these materials from oxidation during prolonged storage. BHT is used as an antioxidant for food, animal feed, petroleum

products, synthetic rubbers, plastics, animal and vegetable oils, and soaps. It serves as an antiskinning agent in paints and inks.

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	- pharmaceuticals, plant protection products, perfumes, fragrances, polishes and wax blends, washing and cleaning products (including solvent based products), biocidal products (e.g disinfectants, pest control), Polymer preparation and compounds, Cosmetics, personal care products - formulation step of life-cycle: Lubricants and lubricant additives : formulation step of life-cycle; Hydraulic fluids Lubricants, greases, release products, Metal working fluids
Uses at industrial sites	- stabilisers, antioxidant In plastics (non-rubber polymers) In rubber products (including tyres) In laboratories - Lubricants, greases, release products Use in machineries (closed system) Use in open systems: Anti-freeze and de-icing products; Leather tanning, dye, finishing, impregnation and care product; Polishes and wax blends; Washing and cleaning products (including solvent products) Use in open high temperature processes- : Metal working fluids Use in Metal working fluid concentrate Use in high energy open processes : metal working fluids
Uses by professional workers	biocidal products(e.g disinfectants, pest control), pharmaceuticals, plant protection products, perfumes, fragrances, polishes and wax blends, washing and cleaning products (including solvent based products), Polymer preparation and compounds, Cosmetics, personal care products – stabilisers, antioxidant Use in plastics (non-rubber polymers) Use in adhesives, coatings, dyes, inks, printing dyes: Adhesives, sealants; Coatings and paints, thinners, paint removes; Ink and toners - Lubricants, greases, release products Use in machineries (closed system): Hydraulic fluids, Use in open systems including anti-freeze, leather, and washing and cleaning products- lubricants Use in high energy open processes- lubricants and lubricant additives:

	metal working fluids In rubber products (including tyres)
Consumer Uses	formulation – stabilizer, antioxidant cosmetics, use in plant protection products (PPP) and biocidal products Use in plastics (non-rubber polymers) :Polymer preparation and compounds; In rubber products (including tyres) :Polymer preparation and compounds Use in adhesives, coatings, dyes, inks, printing dyes : Adhesives, sealants; Coatings and paints, thinners, paint removes; Ink and toners Lubricants, greases, release products Use in machineries (closed system : Hydraulic fluids); Use in open systems including anti-freeze, leather, and washing and cleaning products
Article service life	– stabilisers, antioxidant : Use in plastics (non-rubber polymers): Polymer preparation and compound; In rubber products (including tyres); in machineries Use in fuel (biodiesel)

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[4] ☐ C ☐ M ☐ R	☒ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[4]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[4]	☐ 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)

[4] 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

BHT share common uses with BHA which is in Corap 2015 for ED suspicions an reprotoxic effects but the cross-reading with the BHA is not justified even if the ED profile seems very close between BHT and BHA.
There are some warnings about the potential effect of BHT to disrupt the hormonal system in studies performed on BHT. The overall analysed data show effects on pup survival and pup weight and behavioural effects. However the available data are considered of poor quality and low statiscal power and not sufficient to appropriately manage the risk.

No alert was found on potential endocrine disruptor properties, in particular the steric bulk of BHT molecular structure would not activate estrogenic and androgenic receptors. However there is a concern for thyroid effects but it is currently unclear which mechanistic system is involved in development of liver tumors. Other effects of BHT (hypersensitivity to the worker (skin contact), neurotoxicity of sensitive populations) have also to be examined.

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)

There is a concern for thyroid effects. Induction of hepatic enzyme (CYP 450 cytochrome) has been shown in rodent. It has been proposed (but not proven) that this enzymatic induction would lead to increased thyroïd hormons catabolism. An effect on thyroid physiology in male Wistar rats including an acceleration of iodine cycle is proven. Therefore, the relevance to human of the thyroïd effects needs to be further evaluated.
The results in publications showed BHT can transfer in placenta and can be found in milk in rat that implies to be careful on vulnerable populations (pregnant women and young children). The very few multigenerational studies conducted in rat and mice indicate the occurrence of impaired growth and behavioural effects. This type of alterations can be related to gestational and/or neonatal thyroid disruption but no data is provided for establishing the link in the case of BHT.

Although there is some evidence suggesting that BHT might act on thyroid homeostatis through increased TH hepatic catabolism, in the current knowledge, there is no direct proof that this mechanism is true. As this mechanism is considered as controversial to human, in terms of its physiological consequences, it seems important to (1) validate this hypothetical mechanism in the rat using proper pharmacokinetic and biochemical investigations; (2)check for the occurrence of such mechanisms in animal species and/or *in vitro* system relevant to human in terms of TH specific binding protein, providing that these species will exhibit the same metabolic pattern for BHT than human; (3) check if pregnancy can be a factor of increased sensitivity to this type of mechanisms.

5.5. Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☒ Authorisation	☐ Other (provide further details)
ED properties of BHT will be re-evaluated with appropriate studies. Reprotoxicity (and possibly carcinogenicity) will also be re-evaluated with appropriate studies or appropriate MoA.			