

Justification for the selection of a candidate CoRAP substance

Substance Name (Public Name):	6,6'-di-tert-butyl-4,4'-thiodi-m-cresol
Chemical Group:	Organic
EC Number:	202-525-2
CAS Number:	96-69-5
Submitted by:	Submitted by: Environment Agency Austria on behalf of the Austrian Competent Authority (Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management)
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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

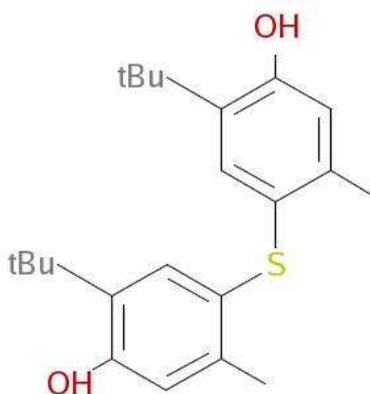
1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	6,6'-di-tert-butyl-4,4'-thiodi-m-cresol
EC number:	202-525-2
EC name:	6,6'-di-tert-butyl-4,4'-thiodi-m-cresol
CAS number (in the EC inventory):	96-69-5
CAS number:	96-69-5
CAS name:	Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-
IUPAC name:	4,4'-sulfanediybis(2-tert-butyl-5-methylphenol)
Index number in Annex VI of the CLP Regulation	---
Molecular formula:	C ₂₂ H ₃₀ O ₂ S
Molecular weight or molecular weight range:	358.5374
Synonyms:	Lowinox TBM-6 Santowhite Crystals Santonox R Sumilizer WX-RC Sumilizer WX-R

Type of substance Mono-constituent Multi-constituent UVCB

Structural formula:



2 CLASSIFICATION AND LABELLING

2.1 Harmonised Classification in Annex VI of the CLP

Not listed.

2.2 Proposal for Harmonised Classification in Annex VI of the CLP

None proposed.

2.3 Self classification

The following self-classifications are given in the registration data:

CLP criteria:

Skin Sens. 1; H317: May cause an allergic skin reaction.

Aquatic Acute 1; H400: very toxic to aquatic life.

Aquatic Chronic 1; H410: very toxic to aquatic life with long lasting effects.

DSD criteria:

N; R50/53: Very toxic to aquatic organisms may cause long-term adverse effects in the aquatic environment.

Xi; R43: may cause sensitisation by skin contact.

The following additional classifications are included in the Classification and Labelling Inventory:

Skin Irrit. 2; H315: Causes skin irritation.

Eye Irrit. 2; H319: Causes serious eye irritation.

STOT SE 3; H335: May cause respiratory irritation.

Repr. 2; H361: Suspected damaging to fertility or the unborn child.

3 JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

3.1 Legal basis for the proposal

- Article 44(1) (refined prioritisation criteria for substance evaluation)
- Article 45(5) (Member State priority)

3.2 Grounds for concern

<input checked="" type="checkbox"/> (Suspected) CMR	<input checked="" type="checkbox"/> Wide dispersive use	<input type="checkbox"/> Cumulative exposure
<input checked="" type="checkbox"/> (Suspected) Sensitiser	<input checked="" type="checkbox"/> Consumer use	<input type="checkbox"/> High RCR
<input checked="" type="checkbox"/> (Suspected) PBT	<input type="checkbox"/> Exposure of sensitive populations	<input type="checkbox"/> Aggregated tonnage
<input checked="" type="checkbox"/> Suspected endocrine disruptor	<input checked="" type="checkbox"/> Other (provide further details below)	

Sensitisation:

In the registration dossier the substance is self-classified for skin sensitization. It is stated that no DNEL is derived as no appropriate quantitative data are available. A qualitative approach is therefore applied mentioning that workers always wear suitable dermal protection equipment and the migration rate from consumer articles is low. This "low" exposure is insufficiently justified within the registration dossier and therefore demonstrates a concern which needs to be clarified. See also the section on exposure below.

Suspected PBT:

The substance was previously being assessed by the UK and was deferred in the Technical Committee for New and Existing Substances PBT working group (PBT no. 113) as a low production volume chemical.

The available screening data shows that the substance is not readily or inherently biodegradable. Therefore it is likely that the substance could fulfil the P and vP criteria, even though no environmental half-life data are available.

The substance has a log Kow of 5.24 and is, thus, meeting the vB screening criterion. The available experimental and some modelled data suggest that the BCF for the substance is <2,000 l/kg. Therefore the substance may not meet the B or vB criteria based on the available data.

However, there are a number of issues that need to be considered further.

- The available BCF study was carried out using relatively high concentrations. These concentrations were close to or above the predicted water solubility of the substance.
- The higher of the two concentrations tested was similar to the short-term LC50 measured in fish. The lower of the two concentrations is close to the 14-day LC50 for fish. Therefore it is not clear if toxicity occurred (or could be expected to have occurred) in this study.
- The substance is taken up across the gut. There is some evidence that transfer to lipids may occur in mammals following oral exposure. Therefore the potential for accumulation in mammals could be higher than so far demonstrated for fish.
- The linear equation included in the REACH guidance predicts a BCF value of 5,675 l/kg.

The available experimental and modelled aquatic toxicity data suggest that the long-term NOEC for this substance is above 0.01 mg/l. However, many of the acute studies were conducted at concentrations above the predicted water solubility of the substance, and so the conclusion that the substance would not be expected to meet the T-criterion based on these data can only be tentative.

The classification for human health given in the registration dossiers does not lead to the T-criterion being met. However, the classification and labeling inventory include for this substance the classification Repro 2. (Hazard Statement H361). This classification, if confirmed, would meet the T-criterion.

Suspected CMR: Reproductive toxicity

Waiving of a fertility study is insufficiently justified. It is stated that because no effects on reproductive organs were seen in repeated dose studies in rats and mice (NTP, 1994) a fertility study can be waived at the present tonnage band. However, a study from the open literature (Takahashi & Oishi, 2006; not cited in the registration dossier) demonstrated effects on male reproductive organs (dose related decrease in daily sperm production, reduced weight of male reproductive organs, severe exfoliation of seminiferous tubules and sloughing of seminiferous tubules) in rats and mice. No NOAEL could be derived (LOAEL = 41 mg/kg bw/day).

There are 2 developmental toxicity studies cited in the dossier, both having major deficiencies. One is a screening study testing only one dose, the LD10, in mice. Next to maternal death reduced pup survival was observed. A non-GLP study was conducted in rabbits. In the registration dossier this study is interpreted to give no indications for developmental effects. In contrast the USEPA (2010) derived a LOAEL of 2mg/kg bw/day for developmental effects (decreased mean pup weight and litter size), with a NOAEL of 0,2mg/kg bw/day. The NOAEL for maternal toxicity was 2mg/kg bw/day (with anorexia and abortions at the LOAEL of 20mg/kg bw/day). Minor skeletal and visceral malformations were also seen in the pups.

Suspected endocrine disrupter:

Takahashi & Oishi (2006; not cited in the registration dossier) demonstrated effects on male reproductive organs and sperm production in rats and mice. They also tested the substance in an uterotrophic assay in ovariectomised mice and found positive results. They concluded that the effects on male reproductive organs might be caused by an estrogenic mechanism.

Other:

- Immunotoxic effects:

Publications from the open literature (Holsapple et al., 1988; cited in the registration dossier; Munson et al., 1988; not cited in the registration dossier) report immunotoxic effects in rats at the lowest dose tested (i.e.10 mg/kg bw/day). These effects are supported by findings on thymus, spleen and lymphnodes from repeated dose studies included in the registration dossier.

- Human and environmental exposure:

A quantitative exposure assessment for man was not prepared, as it is stated that dermal and inhalation exposure can be completely excluded by applying the effective risk management measures that are proposed. Regarding the description of uses, exposure scenarios and risk management measures, the statement of complete exclusion referring to the given description is doubted and considered to be a concern.

The calculated RCRs for freshwater and marine water sediment are close to one. Therefore, it needs to be checked, if the PEC and PNEC derivations are prepared in a proper way.

3.3 Information on aggregated tonnage and uses

<input type="checkbox"/> 1 – 10 tpa	<input type="checkbox"/> 10 – 100 tpa	<input checked="" type="checkbox"/> 100 – 1000 tpa
<input type="checkbox"/> 1000 – 10,000 tpa	<input type="checkbox"/> 10,000 – 100,000 tpa	
<input type="checkbox"/> 100,000 – 1000,000 tpa	<input type="checkbox"/> > 1000,000 tpa	
<input type="checkbox"/> Confidential		
<input checked="" type="checkbox"/> Industrial use		
<input checked="" type="checkbox"/> Professional use		
<input checked="" type="checkbox"/> Consumer use		
<input type="checkbox"/> Closed System		
Manufacture / Formulation		
Identified Use (IU) name	Substance supplied to that use	Use descriptors
Manufacture of 4,4'-sulfanediylbis (2-tert-butyl-5-methylphenol), including distribution, storing, handling and quality control	as such (substance itself)	<p>Process category (PROC):</p> <p>PROC 1: Use in closed process, no likelihood of exposure</p> <p>PROC 3: Use in closed batch process (synthesis or formulation)</p> <p>PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities</p> <p>PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities</p> <p>PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)</p> <p>Environmental release category (ERC):</p> <p>ERC 1: Manufacture of substances</p>
Formulation of non-dusting blends (NDB)	as such (substance itself)	<p>Process category (PROC):</p> <p>PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)</p> <p>PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities</p> <p>PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)</p> <p>PROC 14: Production of preparations or articles by tableting, compression, extrusion, pelletisation</p> <p>PROC 21: Low energy manipulation of substances bound in materials and/or articles</p> <p>PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles</p> <p>Market sector by type of chemical product:</p> <p>PC 32: Polymer preparations and compounds</p>

		<p>Environmental release category (ERC): ERC 2: Formulation of preparations</p>
<p>Formulation of aqueous dispersions</p>	<p>as such (substance itself)</p>	<p>Process category (PROC): PROC 3: Use in closed batch process (synthesis or formulation)</p> <p>Market sector by type of chemical product: PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC): ERC 2: Formulation of preparations</p>
<p>Uses at Industrial sites</p>		
<p>Use as anti-oxidant in medium/high voltage cross-linked PE cables</p>	<p>as such (substance itself)</p> <p>in a mixture</p>	<p>Process category (PROC): PROC 3: Use in closed batch process (synthesis or formulation)</p> <p>PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)</p> <p>PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities</p> <p>PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)</p> <p>PROC 13: Treatment of articles by dipping and pouring</p> <p>PROC 14: Production of preparations or articles by tableting, compression, extrusion, pelletisation</p> <p>PROC 21: Low energy manipulation of substances bound in materials and/or articles</p> <p>PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles</p> <p>Market sector by type of chemical product: PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC): ERC 3: Formulation in materials ERC 5: Industrial use resulting in inclusion into or onto a matrix</p> <p>Sector of end use (SU): SU 12: Manufacture of plastics products, including compounding and conversion</p> <p>Subsequent service life relevant for that use?: yes</p>
<p>Industrial use as anti-oxidant/bleaching agent in adhesives and emulsifiers for rubber emulsion</p>	<p>as such (substance itself)</p>	<p>Process category (PROC): PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)</p> <p>PROC 10: Roller application or brushing</p> <p>PROC 14: Production of preparations or articles by</p>

		<p>tableting, compression, extrusion, pelletisation</p> <p>Market sector by type of chemical product: PC 1: Adhesives, sealants PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC): ERC 3: Formulation in materials ERC 5: Industrial use resulting in inclusion into or onto a matrix</p> <p>Sector of end use (SU): SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 11: Manufacture of rubber products</p> <p>Subsequent service life relevant for that use?: yes</p>
<p>Use in the production of impact modified plastic and thermoplastics articles</p>	<p>as such (substance itself) in a mixture</p>	<p>Process category (PROC): PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tableting, compression, extrusion, pelletisation PROC 21: Low energy manipulation of substances bound in materials and/or articles PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles</p> <p>Market sector by type of chemical product: PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC): ERC 3: Formulation in materials ERC 5: Industrial use resulting in inclusion into or onto a matrix</p> <p>Sector of end use (SU): SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 11: Manufacture of rubber products SU 12: Manufacture of plastics products, including compounding and conversion</p> <p>Subsequent service life relevant for that use?: yes</p>

<p>Manufacture of resins</p>		<p>Process category (PROC):</p> <p>PROC 2: Use in closed, continuous process with occasional controlled exposure</p> <p>PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises</p> <p>PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities</p> <p>PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)</p> <p>PROC 12: Use of blowing agents in manufacture of foam</p> <p>PROC 13: Treatment of articles by dipping and pouring</p> <p>PROC 14: Production of preparations or articles by tableting, compression, extrusion, pelletisation</p> <p>Market sector by type of chemical product:</p> <p>PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC):</p> <p>ERC 3: Formulation in materials</p> <p>ERC5 – Industrial use resulting in inclusion into or onto a matrix</p> <p>ERC 6c: Industrial use of monomers for manufacture of thermoplastics</p> <p>Sector of end use (SU):</p> <p>SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)</p> <p>SU 12: Manufacture of plastics products, including compounding and conversion</p> <p>Subsequent service life relevant for that use?: yes</p>
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Uses by professional workers

<p>Identified Use (IU) name</p>	<p>Substance supplied to that use</p>	<p>Use descriptors</p>
<p>Professional use of adhesives and emulsifiers</p>		<p>Process category (PROC):</p> <p>PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)</p> <p>PROC 10: Roller application or brushing</p> <p>PROC 14: Production of preparations or articles by tableting, compression, extrusion, pelletisation</p> <p>Market sector by type of chemical product:</p>

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		<p>PC 1: Adhesives, sealants</p> <p>PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC):</p> <p>ERC 3: Formulation in materials</p> <p>ERC 5: Industrial use resulting in inclusion into or onto a matrix</p> <p>Subsequent service life relevant for that use?: yes</p>
Professional use of 4,4'-sulfanediylbis (2-tert-butyl-5-methylphenol) in R&D	as such (substance itself)	<p>Process category (PROC):</p> <p>PROC 15: Use as laboratory reagent</p> <p>Market sector by type of chemical product:</p> <p>PC 21: Laboratory chemicals</p> <p>Environmental release category (ERC):</p> <p>ERC 8a: Wide dispersive indoor use of processing aids in open systems</p> <p>ERC 8b: Wide dispersive indoor use of reactive substances in open systems</p> <p>Subsequent service life relevant for that use?: yes</p>
Professional use of 4,4'-sulfanediylbis (2-tert-butyl-5-methylphenol) in R&D	In a mixture	<p>Process category (PROC):</p> <p>PROC 15: Use as laboratory reagent</p> <p>Market sector by type of chemical product:</p> <p>PC 21: Laboratory chemicals</p> <p>Environmental release category (ERC):</p> <p>ERC 8a: Wide dispersive indoor use of processing aids in open systems</p> <p>ERC 8b: Wide dispersive indoor use of reactive substances in open systems</p> <p>Sector of end use (SU):</p> <p>SU 24: Scientific research and development</p> <p>Subsequent service life relevant for that use?: No</p>

Consumer Uses

Identified Use (IU) name	Use descriptors
Consumer use of adhesives and emulsifiers	<p>Chemical product category (PC):</p> <p>PC 1: Adhesives, sealants</p> <p>PC 32: Polymer preparations and compounds</p> <p>Environmental release category (ERC):</p> <p>ERC 5: Industrial use resulting in inclusion into or onto a matrix</p> <p>ERC 3: Formulation in materials</p> <p>Subsequent service life relevant for that use?: yes</p>
Service life consumers	Environmental release category (ERC):

	<p>ERC 10a: Wide dispersive outdoor use of long-life articles and materials with low release</p> <p>ERC11a – Wide dispersive indoor use of long-life articles and materials with low release</p> <p>Subsequent service life relevant for that use?: no</p>
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3.4 Other completed/ongoing regulatory processes that may affect suitability for substance evaluation

<input type="checkbox"/> Compliance check final decision	<input type="checkbox"/> Dangerous substances Directive 67/548/EEC
<input type="checkbox"/> Testing proposal	<input type="checkbox"/> Existing Substances Regulation 793/93/EEC
<input type="checkbox"/> Annex VI (CLP)	<input type="checkbox"/> Plant Protection Products Regulation 91/414/EEC
<input type="checkbox"/> Annex XV (SVHC)	<input type="checkbox"/> Biocidal Products Directive 98/8/EEC
<input type="checkbox"/> Annex XIV (Authorisation)	<input type="checkbox"/> Other (provide further details below)
<input type="checkbox"/> Annex XVII (Restriction)	
Not covered in any of these processes.	

3.5 Information to be requested to clarify the suspected risk

<input checked="" type="checkbox"/> Information on toxicological properties	<input type="checkbox"/> Information on physico-chemical properties
<input type="checkbox"/> Information on fate and behaviour	<input checked="" type="checkbox"/> Information on exposure
<input checked="" type="checkbox"/> Information on ecotoxicological properties	<input type="checkbox"/> Information on uses
<input type="checkbox"/> Other (provide further details below)	
<p><u>Toxicological properties:</u></p> <p>Fertility study/EOGRTS – information on possible reproductive as well as endocrine disrupting effects.</p> <p>The inclusion of a DIT cohort in an EOGRTS protocol might shed light on the effects seen in animals exposed during gestation and on the observed immunotoxic effects. Inclusion of parameters relevant for the detection of possible estrogenic effects within the EOGRTS protocol (e.g. female cyclicity, ...) could be considered in order to clarify the identified concerns.</p> <p>Special investigations like e.g. the effects of the substance on testicular enzymes or mechanistic studies of the potential estrogenic mechanism (e.g. Reporter assays) could be considered.</p> <p><u>Ecotoxicological properties:</u></p> <p>Long-term toxicity on fish</p> <p><u>Information on exposure:</u></p> <p>More detailed description of the needed risk management measures for safe use regarding human and environment</p> <p>Validation/justification of the provided assumptions and conclusions used in the assessment.</p>	

3.6 Potential follow-up and link to risk management

<input checked="" type="checkbox"/> Restriction	<input checked="" type="checkbox"/> Harmonised C&L	<input checked="" type="checkbox"/> Authorisation	<input type="checkbox"/> Other (provide further details)
<p>Depending on the outcome of the evaluation it might be justified to prepare a CLH dossier. Potential classification as STOT RE for immunotoxic effects and / or reproductive toxicity.</p> <p>If the evaluation demonstrates RCRs > 1 the evaluation might result in the preparation of a restriction or SVHC dossier.</p>			

4 REFERENCES:

Holsapple MP, White KL Jr, McCay JA, Bradley SG, Munson AE. (1988): An immunotoxicological evaluation of 4,4'-thiobis-(6-t-butyl-m-cresol) in female B6C3F1 mice. 2. Humoral and cell-mediated immunity, macrophage function and host resistance. *Fundam Appl Toxicol.* 1988 May;10(4):701-16.

Munson AE, White KL Jr, Barnes DW, Musgrove DL, Lysy HH, Holsapple MP (1988): An immunotoxicological evaluation of 4,4'-thiobis-(6-t-butyl-m-cresol) in female B6C3F1 mice. 2. Body and organ weights, hematology, serum chemistries, bone marrow cellularity, and hepatic microsomal parameters. *Fundam Appl Toxicol.* 1988 May;10(4):691-700.

NTP (1994): NTP technical report on the toxicology and carcinogenesis studies of 4,4'-thiobis(6-t-butyl-m-cresol)(CAS 96-69-5) in F344/N rats and B6C3F1 mice (feed studies). NTP TR 435.

Takahashi O, Oishi S. (2006): Male reproductive toxicity of four bisphenol antioxidants in mice and rats and their estrogenic effect. *Arch Toxicol.* 2006 Apr;80(4):225-41.

US EPA (2010): Hazard Characterization Document: Screening-level hazard characterization, Bridged Alkyl Phenol Category (http://www.epa.gov/chemrtk/hpvis/hazchar/Category_Bridged%20Alkyl%20Phenol_June%202010.pdf)