# Justification Document for the Selection of a CoRAP Substance

**Substance Name (public name):** 4-(4-isopropoxyphenylsulfonyl)phenol

| | |
|---|---|
| **EC Number:** | 405-520-5 |
| **CAS Number:** | 95235-30-6 |
| **Authority:** | BE CA |
| **Date:** | 19/03/2019 |

**Cover Note**

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

## Table of Contents

# 1 IDENTITY OF THE SUBSTANCE

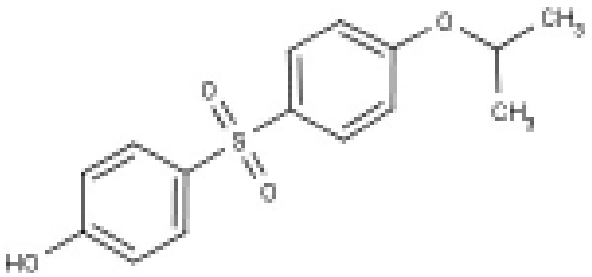
## 1.1 Other identifiers of the substance

**Table: Other Substance identifiers**

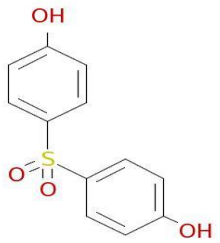
| | |
|---|---|
| **EC name (public):** | 4-(4-isopropoxyphenylsulfonyl)phenol |
| **IUPAC name (public):** | 4-[4-(propan-2-yloxy)benzenesulfonyl]phenol |
| **Index number in Annex VI of the CLP Regulation:** | 604-046-00-8 |
| **Molecular formula:** | $C_{15}H_{16}O_4S$ |
| **Molecular weight or molecular weight range:** | 292 g/mol |
| **Synonyms:** | D-8<br>DD-8<br>4-hydroxy-4'-isopropoxydiphenyl sulfone |

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

**Structural formula:**




## 1.2 Similar substances/grouping possibilities

| Name | EC | structural formula |
|---|---|---|
| 4,4'-sulfonyldiphenol | 201-250-5 |  |

# 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<br>Regulation (EC) No 1107/2009 | |
| | ☐ Biocidal Product Regulation<br>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 | / | |

[1] Please specify the relevant entry.

# 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) | | |
| **604-046-00-8** | **4-(4-isopropoxyphenylsulfonyl)phenol** | 405-520-5 | 95235-30-6 | **Aquatic Chronic 2** | **H411** | | |

### 3.1.2 Self classification

- In the registration:

  Same as the harmonized classification

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

  NA

### 3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

NA

# 4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[2]

## 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 |
| NONS dossier | | |

*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

**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** | / |
| **Uses at industrial sites** | Manufacture of paper and paper products |

[2] *Dissemination website consulted on 30 May 2018*

| | |
|---|---|
| **Uses by professional workers** | / |
| **Consumer Uses** | |
| **Article service life** | Thermal paper |

# 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<br>☐ C ☐ M ☐ R | Suspected CMR[1]<br>☐ C ☐ M ☐ R | ☒ Potential endocrine disruptor |
| ☐ Sensitiser | ☐ Suspected Sensitiser[3] | |
| ☐ 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) |
| The substance shows anti-estrogenic effects in at least one in vitro assay (Kuruto-Niwa *et al*., 2005)<br>Preliminary results from a screening study indicated very low estrogenic activity for D-8 after analysis using a cell-based bioassay testing (Björnsdotter *et al*, 2017). Estrogenicity of D-8 was reported to be negative in a yeast two-hybrid assay and in an estrogen receptor competitive enzyme-linked immunosorbent assay (Terasaki *et al*. 2007). | | |

In silico, VirtualToxLab showed a relatively low binding affinity of D-8 to estrogen and (1,33 µM for Estrogen receptor β and 2,01 µM for Estrogen receptor α) androgen receptors (7,93 µM), especially compared to Bisphenol A (Goldinger *et al*, 2015).

Endocrine disruptome (prediction tool that uses molecular docking to predict binding of compounds to 14 different human nuclear receptors) indicated a medium probability of binding to AR an, GR, TRα, TRβ

D-8 shows structural similarity with bisphenol S. Instead of the two phenols of bisphenol S, D-8 has one phenol and an isopropoxy-group in para on the other benzene-ring. There is a potential for fragmentation of this function releasing a charged form, very similar to Bisphenol S. No toxicokinetic data is however available for D-8.

Exposure to 100 µM of D-8 (29 mg/L) induced, already after 24 hpf, abnormal developmental effects in zebrafish embryos, similar to Bisphenol A and TGSA (4,4'-sulfonylbis(2-allylphenol)) (Björnsdotter *et al*, 2017). No definite conclusion can however be drawn based on the results of this screening test.

In vitro assays were performed on D-8 itself. Based on the structure and the available in vivo data, ED effects of the substance or its metabolite(s) cannot be ruled out.

Other: Clarification of the uses of the substance

4-(4-isopropoxyphenylsulfonyl)phenol (D-8) has been found in thermal paper as a color developer in Germany and Switzerland (Eckardt & Simat, 2017 ; Goldinger *et al*, 2015). Moreover, an American study showed that D-8 has been found in urine and blood of cashiers after exposure to handle receipts, demonstrating that thermal receipt paper is a potential source of occupational exposure of D-8 (Thayer *et al.* 2016).

D-8 has also been identified as an environmental pollutant in paper-recycling process water (Terasaki *et al*, 2007).

*References*

Björnsdotter M.K., Jonker W. Legradi J., Kool J. Ballesteros-GÓmez A. (2017) Bisphenol A alternatives in thermal paper from the Netherlands, Spain, Sweden and Norway. Screening and potential toxicity. Science of the Total Environment, 601-602, 210-221.

Eckardt M and Simat T.J. (2017) Bisphenol A and alternatives in thermal paper receipts – a German market analysis from 2015 to 2017. Chemosphere, 186, 1016-1025

Goldinger D.M., Demierre A-L., Zoller O., Rupp H., Reinhard H., Magnin R., Becker T.W., Bourqui-Pittet M. (2015) Endocrine activity of alternatives to BPA found in thermal paper in Switzerland. Regulatory Toxicology and Pharmacology, 71, 453-462.

Kuruto-Niwa R., Nozawa R., Miyakoshi T., Shiozawa T and Terao Y. (2005) Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system. Environmental Toxicology and Pharmacology, 19, 121-130

Terasaki M., Shiraishi F., Fukazawa H. and Makino M. (2007) Occurrence and estrogenicity of phenolics in paper-recycling process water: pollutants originating from thermal paper in waste paper. Environmental Toxicology and Chemistry, 26, 2356-2366.

Thayer K.A., Taylor K.W., Garantziotis S., Schurman S.H., Kissling G.E., Hunt D., Herbert B., Church R., Jankowich R., Churchwell M.I., Scheri R.C., Birnbaum L.S. and Bucher J.R. (2016) Bisphenol A, bisphenol S, and 4-hydroxyphenyl 4-

[3] 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

isoprooxyphenylsulfone (BPSIP) in urine and blood of cashiers. Environ Health Perspect 12, 437-444; http://dx.doi.org/10.1289/ehp.1409427

## 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) |
| Further data is needed to assess the possible ED properties of D-8 (toxicokinetics, ED for fish…) as explained in section 5.3.<br><br>Further clarification of the uses of the substance might be requested. | |

## 5.5. Potential follow-up and link to risk management

| | | | |
|---|---|---|---|
| ☐ Harmonised C&L | ☐ Restriction | ☒ Authorisation | ☐ Other (provide further details) |
| If the analysis/requested study results indicate that D-8 and/or its metabolite(s) are ED(s), identification as SVHC according to art.57(f) of REACH will be considered as potential follow-up RMM. | | | |