Bundesministerium
Klimaschutz, Umwelt,
Energie, Mobilität,
Innovation und Technologie

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Bis(4-chlorophenyl) sulphone

EC No 201-247-9

CAS No 80-07-9

Evaluating Member State: Austria

Dated: 02. 12. 2020

Evaluating Member State Competent Authority

Austrian MSCA:
Austrian Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology Radetzkystraße 2, 1030 Vienna, Austria

The evaluation was performed by:
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Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Bis(4-chlorophenyl) sulphone (BCPS - EC number 201-247-9, CAS RN 80-07-9) was originally selected for substance evaluation in order to clarify concerns about:

- suspected PBT/vPvB

- wide dispersive use

- aggregated tonnage

During the evaluation, concerns for endocrine disruption, reproductive toxicity, mutagenicity, eye irritation, and repeated dose toxicity were identified. In addition, the need for correct classification for the environment was notified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

- Targeted Compliance check concluded, final decision 27.08.2014, Decision´s deadline 04.12.2014. The requested analytical data have been provided.

- Two Testing proposals:

  - First Testing proposal (TPEs), concluded, Decision date 31.05.2013. Decision´s deadline 31.05. 2014.[2] The requested data have been provided.
  - Second Testing Proposal (TPE-076/2018), information requested: Toxicity to reproduction, discussed at MSC-62, 2018; decision date: 30.01.2019, Registrant(s) are requested to carry out an EOGRTS (OECD TG 443) in rats, decision´s deadline for data submission: 6. August 2021[3].

- Food Contact Material - Regulation (Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food): BCPS is listed in the Union list. The specific migration limit (SML) is 0.05 mg/kg. FCM substance No. 152, Ref. No. 15610.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level to be discussed in an RMOA	x
Harmonised Classification and Labelling	-
Identification as SVHC (authorisation)	(x)
Restrictions	(x)
Other EU-wide measures	-
No need for regulatory follow-up action at EU level	-

[2] https://echa.europa.eu/documents/10162/02798d91-5265-8620-b42a-59e8701ab288
[3] https://echa.europa.eu/documents/10162/e12106b0-ca86-dbcc-2373-b3c2329738a9

In chapter 4 more considerations are provided on potential follow-up regulatory actions at EU level.

In chapter 5 more considerations are provided on those concerns for which (currently) no follow up is considered necessary.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

The need to consider the following risk management measures will be discussed in an RMO analysis and the appropriate conclusions will be drawn.

4.1.1. Harmonised Classification and Labelling

No harmonised classification is proposed at the moment.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

BCPS is fulfilling the criteria for a substance of very high concern as the substance comprises vPvB properties in accordance to art. 57e) of REACH. The vP criterion is fulfilled based on reliable half-life data obtained from a water / sediment simulation test (OECD TG 308). BCPS fulfils the vB criterion based on a WoE approach, as BCPS is taken up and detected in various wildlife species. High BCPS levels were found especially in top predators like fish-eating bird eggs and marine mammals like seals. Field BMF values are > 1, half-life in adipose tissue in rats is very long after single exposure and the substance is detected in human liver.

4.1.3. Restriction

Restrictions may be introduced, when there is an unacceptable risk to human health or the environment arising from the manufacture, placing on the market and use of a substance, and the risk needs to be addressed on a Community-wide basis. As shown by monitoring data, this substance with vPvB properties is occurring in the European environment (biota and aquatic compartment). Therefore restriction might be an appropriate option requiring further consideration in an RMOA.

4.1.4. Other EU-wide regulatory risk management measures

Not considered to be needed at this stage.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

No follow up for the human health concerns on endocrine disruption and reproductive toxicity are planned at the moment as a testing proposal decision, requesting provision of an EOGRTS by 06 August 2021, was notified to the Registrant(s). This study will provide further insight regarding the potential endocrine disrupting properties for BCPS.

Moreover, the concern for developmental neurotoxicity based on neurotoxic effects of structural analogues like polychlorinated biphenyls and the indications for an endocrine mode of action relevant for brain development is currently not followed up as the results from the ongoing EOGRTS are awaited.

Nevertheless, it is concluded that for BCPS a concern is identified for possible endocrine disrupting properties for aquatic vertebrates. However, this concern is not followed up at the moment, as considerations regarding identification of BCPS as a vPvB substance according to Art. 57e) of REACH are envisaged to be part of the RMOA proposed.

Currently BCPS has no harmonised classification. The registrants self-classify BCPS for Eye Irrit. Cat. 2 and for Aquatic Chronic 2 according to classification criteria laid down in Regulation 1272/2008/EC (CLP Regulation). At the moment no harmonised classification is proposed.

5.1. No need for regulatory follow-up at EU level

The repeated dose toxicity concern has been clarified during substance evaluation.

Table 2

REASON FOR REMOVED CONCERN The concern(s) could be removed because	Tick box
Clarification of hazard properties/exposure	x
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

The liver effects are considered to be adaptive responses caused by liver enzyme induction, resulting in adverse liver effects only at doses above the limit value for classification according to CLP. Evaluation of the data reveals that the CLP criteria for classification are not fulfilled.

The eMSCA concludes that there is insufficient evidence to support a classification of the substance for Muta. Cat. 2. Further animal testing is not proposed since the existing data suggests a rather low concern for mutagenic activity.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 3

FOLLOW-UP Follow-up action	Date for intention	Actor
RMOA	2021+	MS actor was requested by ECHA, but not yet confirmed

Part B. SUBSTANCE EVALUATION

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Bis(4-chlorophenyl) sulphone (BCPS) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB

- Wide dispersive use

- Aggregated tonnage

During the evaluation concerns for endocrine disruption, reproductive toxicity, mutagenicity and repeated dose toxicity were identified. In addition, the need for correct classification for the environment was notified.

Table 4 Overview on relevant BCPS properties

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
PBT/vPvB	BCPS is not readily biodegradable and meets the screening criteria P and vP. Based on reliable half-life data obtained from a water / sediment simulation test according to OECD TG 308, BCPS meets the vP criteria in Annex XIII of REACH. Using a weight of evidence assessment of the data available, BCPS meets the vB criteria in Annex XIII of REACH: • BCPS is taken up and detected in various wildlife species • High BCPS levels in fish-eating bird eggs (mean: 1136 ng/g l.w.) and seals (median: 200 ng/g l.w.) • Field BMF values (fish, bird) > 1 • Field BMF values (fish, seals) > 1 • Very long half-life in rats (high affinity to adipose tissue) • Detection in human liver Several data are available on human health and ecotoxicity for BCPS. Based on the currently available data, no conclusion on the T-criterion is currently possible.
Environmental classification	Based on the observed NOEC values from both the long-term daphnid reproduction study (0.32 mg/L) and algal growth inhibition study (0.28 mg/L) on BCPS, and the non-rapid biodegradability of the substance, the environmental hazard classification should be Aquatic Chronic 2 in accordance with EC Regulation 1272/2008. After discussions with the Registrant(s) in the course of this substance evaluation the classification was updated from Aquatic Chronic 4 to Aquatic Chronic 2 by the Registrant(s). No harmonised classification is proposed at the moment.
Repeated dose toxicity	Repeated dose toxicity studies demonstrate that liver is a target organ of BCPS toxicity, characterised by centrilobular hepatocyte

	hypertrophy, bile ducte hyperplasia and centrilobular degeneration. At higher doses increased kidney weight, increased incidence of nephropathy and decreased thymus weight were evident. Classification as STOT RE is not warranted as the observed effects are not considered severe enough at relevant doses.
Mutagenicity	There is insufficient evidence to support a classification of the substance for mutagenicity and long term carcinogenicity studies do not demonstrate any carcinogenic properties.
Reproductive, immuno- and neurotoxicity, endocrine disruption	Increase in testes weight was evident in several studies and epididymis weight increase in one study. In these studies liver is a target organ of toxicity and the increase in testes weight was observed only at higher concentrations than liver weight increase. However, so far, there is no evidence that these effects are interlinked. Some evidence that BCPS might have an impact on testes also comes from the carcinogenicity study in rats. Malignant mesothelioma originating from tissues covering the testes and the epididymides was observed in treated animals. Also, changes in uterus and ovary weights were observed in mice. Moreover, statistically significant reductions in thymus weight as well as some effects on hindlimb activity were observed. An EOGRTS with the cohorts 1A and 1B (Reproductive toxicity) and cohort 3 (Developmental immunotoxicity: due to observed effects on thymus) has been requested via a testing proposal Decision. Based on the available in silico, in vitro and in vivo data it is concluded that BCPS has the potential for endocrine disrupting properties for aquatic vertebrates. This concern is not followed up at the moment, as the identification of BCPS as a vPvB substance according to Art. 57e) of REACH is proposed. This risk management measure is currently considered sufficient to cover also any concerns arising from endocrine disrupting properties for aquatic vertebrates. It is concluded that there are concerns for reproductive toxicity, developmental immuno- and neurotoxicity as well as for endocrine disruption for human health. Nevertheless, as an EOGRTS is requested via a testing proposal Decision and should be available by August 2021, more information relevant for these concerns will be presumably available.
Eye irritation	Available key eye irritation study has significant deviations from OECD TG 405 (Acute Eye Irritation/Corrosion). Mean cornea and iris scores were 1 and mean conjunctivae and chemosis scores were 2 in all tested animals (24h, 48h, 72h after application). At the end of the observation period, chemosis and iris effects had resolved. Cornea (score 1 in 1/3 animals) and conjunctivae effects (score 1 in 3/3 animals) were not fully reversible. Also scar formation was noted in all test animals at 48h and subsequent readings. The scar formation at the end of the observation period might be evidence that the effect is irreversible; nevertheless, due to short post-application period no definitive conclusion can be drawn on reversibility of the effect. The eMSCA supports the Registrants conclusion that BCPS is eye irritative and a classification according to Regulation 1272/2008/EC for Eye Irrit. Cat. 2 is warranted. No harmonised classification is proposed at the moment.

Other elements to be considered	Apart from the above mentioned intrinsic vPvB properties of the substance additional concerns need to be considered: • Mobility: The substance is considered as mobile and the main environmental transport will take place in water and not in air, nevertheless the ultimate sink of BCPS seems to be the sediment. BCPS can be efficiently distributed throughout the aquatic environment, including groundwater; BCPS has the potential to contaminate drinking water. • Insecticidal activity: BCPS has an insecticidal activity, which is in the same range as DDT (Misra et al., 1957) at least to fly. • Long-range transport potential (LRTP): BCPS has a calculated DT_{50} in air of 54.6 days indicating a potential for long range atmospheric transport (AOPWIN v1.92), therefore a model was used to estimate the LRTP. The multimedia OECD model results indicate a similar potential of LRT as the POP reference chemical γ-HCH.

7.2. Procedure

Evaluation of Bis(4-chlorophenyl) sulphone (BCPS) was launched in March 2019. The Registrants of this substance were contacted before start of evaluation and asked to support the evaluation by providing the original studies used for the individual registrations. The Registrants confirmed support and provided these studies. In a first step, the performed evaluation of BCPS was not targeted and covered all sections of the chemical safety assessment. In a second step, Evaluation was focused on the areas of concern-identified prior and during evaluation. Studies provided by the Registrants, public available studies/data, studies for reference substances and QSARs were used by the eMSCA for assessment and conclusion. Based on the available data in total, no need for new data was identified. The available information was considered sufficient to clarify the identified concerns without a need to request further information. Evaluation of BCPS was closed in March 2020.

This document containing a conclusion document (Part A) and a substance evaluation report (Part B) was finalized in August 2020. Key elements and outcome of the evaluation are summarized. Confidential information is anonymized or presented in the confidential annexes not available for the public.

7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Bis(4-chlorophenyl)sulphone
EC number:	201-247-9
CAS number:	80-07-9
Index number in Annex VI of the CLP Regulation:	None
Molecular formula:	$C_{12}H_8Cl_2O_2S$
Molecular weight range:	287.1617 g/mole

Synonyms:	Sulfone, bis(p-Chlorophenyl) 1,1'-Sulfonylbis(4-chlorobenzene) 4,4'-Dichlorodiphenyl sulfone 4,4'-Dichlorodiphenyl sulphone 4-Chlorophenyl sulfone Benzene, 1,1'-sulfonylbis(4-chloro- Bis(4-chlorophenyl) sulfone Bis(4-chlorophenyl) sulphone Di-p-chlorophenyl sulfone p,p'-Dichlorodiphenyl sulfone p-Chlorophenyl sulfone Sulfone, bis(p-chlorophenyl) BCPS DCDPS

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

Structural formula:

Other relevant information about substance composition

No impurities and additives are listed for the substance on the ECHA dissemination site (https://echa.europa.eu/de/brief-profile/-/briefprofile/100.001.135; 16.01, 2019). Further information can be found in the confidential Annex.

7.4. Physico-chemical properties

The following values are taken from ECHA's dissemination site (12. 08. 2019).

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	*Substance is a white, odourless solid.*
Melting point	*between 147 °C - 150 °C*

Boiling point	*397°C, decomposition closely to boiling temperature*
Density	*1.504 ± 0.001 g/cm³ (= 1504 kg/m³) at 20.2°C*
Vapour pressure	*$5.1x10^{-6}$ Pa at 20°C* *Experimental values were obtained in a guideline study under GLP according to OECD TGD 104 or EU TGD A.4. In application of the gas saturation method the vapour pressure was measured at 50, 60 and 70 °C. By extrapolation the values of $1.50x10^{-5}$ Pa at 25 °C, $5.1x10^{-6}$ Pa at 20 °C and $1.2x10^{-6}$ Pa at 12 °C were derived.*
Water solubility	*0.86 mg/L at 20°C* *Water solubility has been determined under GLP according to OECD TGD 105 with the column elution method. A value of 0.86 mg/L at 20 °C at a pH from 5.5 to 6 was measured.*
Partition coefficient n-octanol/water (Log Kow)	*3.9 at 20°C* *Based on an experimental result from study under GLP using the shake flask method according to OECD TGD 107 the log K_{ow} of BCPS is determined to be 3.9.*
Flammability	*Non flammable*
Explosive properties	*Non explosive*
Oxidising properties	*No oxidising properties*
Granulometry	*particles <100µm approximate 7.5%, particles <10µm approximate 0%, particles <4µm approximate 0%* *The particle size distribution of BCPSpowder was determined similar to OECD TGD 110 and ISO 13320-1 methods under non-GLP conditions. About 7.5% of BCPS belongs to inhalable fraction. No respirable fraction was identified.* *The dustiness of the powder is classified as "medium" due to the particle size distribution (D10=115 µm, D50=240 µm, D90=561 µm). The dustiness of the pellets is classified as "low" because the pellets are not dusty.*
Stability in organic solvents and identity of relevant degradation products	*Stable*
Dissociation constant	*BCPS does not contain an ionisable functionality. Therefore, dissociation is not expected to be relevant.*

7.5. Manufacture and uses

7.5.1. Quantities

Bis(4-chlorophenyl)sulphone is manufactured and/or imported in the European Economic Area in 10,000 – 50,000 tons per year.

Table 7

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☒ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Referring to the registration data, BCPS as such is only used industrially as monomere for the production of polymers.
The main polymers are: Polyethersulfon (PESU), Polysulfon (PSU), Polyphenylsulfone (PPSU). Please refer to table 25 for the identity (CAS names and -numbers) of these polymers for more information.

BCPS reacts with the monomers: 4,4'-sulphonyldiphenol (CAS: 80-09-1, Bisphenol S) to form PESU, 4,4'-isopropylidenediphenol (CAS: 80-05-7, Bisphenol A) to form PSU and Biphenyl-4,4'-diol (CAS: 92-88-6) to PPSU. Please refer to table 26 containing the reaction schemes for the manufacture of PSU, PESU and PPSU for more information.

Referring to the common structural diphenyl sulphone group, the polymers reveal various properties at high temperatures and belong to the group of thermoplastics.

The key properties of these high-performance polymers are: high temperature mechanics, excellent hydrolysis resistence, chemical & media stability, transparency, very good fire behavior, good dimensional stability, suitable for food contact and membrane forming. The polymers as such are not suitable for outdoor use, as UV exposure provokes chain scission.

Based on their various properties, the polymers are used for the production of articles from the following sectors/applications (non exhaustive list).

- Automotive sector (e.g. head reflector lamps)
- Aeronautic sector
- Dental applications
- Electric/Electronics components
- Food service
- Hospital goods
- Medical devices
- Microwave cookware
- Piping
- Plumbing applications
- Water pumps
- Oil pumps
- Membranes for food processing and water treatment
- Surgical instrument applications
- Visor for fire helmets

Due to higher sales prices compared to other engineering thermoplastics like polyamides, polyesters and polycarbonates, the applications of these polymers are limited to sophisticated small volume areas like in the electronics, aerospace and medical industries. Processing residues are recycled, but during production the amount of reclaimed material should not exceed 25%[4].

Blending of these polymers for reducing the price of these expensive high-performance polymers for penetrating large volume applications, cannot be ruled out fully in principle. Nevertheless, the Registrant(s) of BCPS considered this to be unlikely for this substance based on their experiences related to such efforts in the past, as the properties of the blends are not comparable to the properties of the pure thermoplastics.

Other uses: there is no clear picture on other uses, but Registrant(s) indicated that BCPS might or have been used for the production of other substances, which are listed below (personal communication, 2019).

- Curing agent in epoxy resins?
- Monomer for Polyetherimides (PEI) or other polymers?

The registrants of BCPS assume (Registrants, 2018, personal communication) that the contamination of the environment with BCPS mainly results from wide dispersive use of agricultural products, which were used in the past. In these products BCPS has been used either as insecticide itself (Tarasenko, et al., 1969) or has been occured as impurity of such products. There is information that technical DDT contained up to 0.03 - 0.6% BCPS (IARC, 1991[5]).

Registration data for BCPS

Referring to the registration data, the substance as such is only used industrially for the production of polymers, rubbers and other chemicals. Professional and consumer uses have not been registered.
The identified use descriptors (Sector of Use: SU, Process Category: PROC, Product Category: PC, Article category: AC, Environmental Release Category: ERC) for the individual uses are given in the table below.
The manufactured articles are used by professionals and consumers.

Table 8 (according to ECHA dissemination site, 07.03.2019)

USES	Use(s)
Uses as intermediate	No registration (date: 05.07.2019)
Manufacture	**PROC 1:** Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions **PROC 3:** Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions **PROC 4:** Chemical production where opportunity for exposure arises

[4] https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwi4rNfbn67qAhVI_qQKHZrlAz8QFjACegQIAhAB&url=https%3A%2F%2Fwww.kunststoffe.de%2Fen%2F_storage%2Fasset%2F589431%2Fstorage%2Fmaster%2Ffile%2F6116872%2Fdownload%2FImpressive%2520Variety%3A%2520Polysulfones%2520(PSU%2C%2520PESU%2C%2520PPSU).pdf&usg=AOvVaw3En4YuLGZw6Hr82lK2fOyE

[5] https://monographs.iarc.fr/wp-content/uploads/2018/06/mono53-9.pdf

	PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities **ERC1:** Manufacture of the substance
Industrial formulation	**PROC 5:** Mixing or blending in batch processes **PROC 8b:** Transfer of substance or mixture (charging and discharging) at dedicated facilities **PROC 9:** Transfer of substance or mixture into small containers (dedicated filling line, including weighing) **PROC 14:** Tabletting, compression, extrusion, pelletisation, granulation **PROC 15:** Use as laboratory reagent **PROC 19:** Hand-mixing with intimate contact and only PPE available. **ERC3:** Formulation into solid matrix **PC 32:** Polymer preparations and compounds
Uses at industrial sites	**Uses covering production of polymers, rubber, use as intermediate (summary)** **Sector of uses covered:** **SU 8:** Manufacture of bulk, large scale chemicals (including petroleum products) **SU 9:** Manufacture of fine chemicals **SU 11:** Manufacture of rubber products **SU 12:** Manufacture of plastics products, including compounding and conversion **Process categories covered:** **PROC 1:** Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions **PROC 3:** Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions **PROC 4:** Chemical production where opportunity for exposure arises **PROC 5:** Mixing or blending in batch processes **PROC 8a:** Transfer of substance or mixture (charging and discharging) at non-dedicated facilities **PROC 8b:** Transfer of substance or mixture (charging and discharging) at dedicated facilities **PROC 14:** Tabletting, compression, extrusion, pelletisation, granulation **PROC 15:** Use as laboratory reagent **PROC 19:** Hand-mixing with intimate contact and only PPE available. **PROC 21:** Low energy manipulation of substances bound in materials and/or articles **Product categories covered:** **PC 19:** Intermediate **PC 32:** Polymer preparations and compounds **Environmental release categories covered:** **ERC5:** Use at industrial site leading to inclusion into/onto article **ERC6a:** Use of intermediate **ERC6c:** Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
Uses by professional workers	Professional uses were not registered.
Consumer Uses	Consumer uses were not registered.

Article service life	***Rubber articles- workers (summary)*** ***AC10g:*** *Other rubber articles* **ERC10a:** Widespread use of articles with low release (outdoor) **ERC11a:** Widespread use of articles with low release (indoor) **ERC12a:** Processing of articles at industrial sites with low release **Rubber articles- consumers** ***AC10g:*** *Other rubber articles* **ERC10a:** Widespread use of articles with low release (outdoor) **ERC11a:** Widespread use of articles with low release (indoor)

Further information:

Drinking water contact substance: BCPS is included in the Belgium positive list[6] of starting materials permitted to produce plastics that may come in contact with drinking water.

Additional use information:

SPIN database

To get a first idea on the distribution of tonnages, information from the SPIN database can be used. The SPIN database[7] summarizes information on substances in different products on the national markets of Norway, Sweden, Finland and Denmark.

Industrial Use (NACE): SE indicated for 2015 11 preparations with 1 Ton with the description "Manufacture of rubber and plastic products".
Industrial Use (National): SE indicated for 2015 11 preparations with 1 Ton with the description "Industry for rubber products"
Use category UC62 "other": The only information found was from Sweden with 1 Ton in 2015.
Use category (National): SE indicted 8 preparations and 1 Ton for the raw materials for production of rubber products.

Swedish Product Register

The Swedish Product Register KemIstat[8] is the search tool for statistics produced by the Swedish Chemicals Inspectorate. The information is based on data in the Products Register and the Pesticide Register. BCPS was found in 2015 in 0.7 tons/year, 2016 in 0 tons per year. The numbers of products were: 10 products 2016 and 12 in products in 2015.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonized classification is reported for BCPS in Annex VI of Regulation (EC) No. 1272/2008 (CLP Regulation).

- In the registration:

  Eye Irrit. 2; H319

[6] http://www.belgaqua.be/document/Positive%20List.pdf

[7] Substances in Preparations in the Nordic countries http://195.215.251.229/DotNetNuke/-default.aspx (accessed 14.2.2019)

[8] http://webapps.kemi.se/kemistat/ (accessed 25.02.2019)

Aquatic Chronic 2; H411

The self classification in the C&L inventory was updated by the Registrants in 2019 to Aquatic Chronic 2; H411.

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

  Aquatic Acute 1; H400 (9 notifications)

  Aquatic Chronic 1; H410 (9 notifications)

  Aquatic Chronic 4; H413 (13 notifications)

  85 notifiers indicate no classification for BCPS (without reasoning) and for 16 CLP notifications no classification was argued based on lack of data.

7.7. Environmental fate properties

7.7.1 Degradation

7.7.1.1. Abiotic degradation

Hydrolysis

The available hydrolysis study with BCPS is performed according to OECD Guideline 111 (Unpublished study report, 2007). No hydrolysis (≤ 10%) of BCPS was observed after 21 days at 50°C. Therefore, the substance is considered to be hydrolytically stable.

Phototransformation/photolysis

No information on the substance.

Phototransformation in air

No experimental data regarding atmospheric degradation have been measured. The half-life of BCPS in the atmosphere was calculated with the AOPWIN program (v.1.92). The half-life is 27.3 days (24-hr day) equal to 54.7 days (12-hr day) assuming a hydroxyl concentration of $5x10^5$ OH/cm^3.

Phototransformation in water

No data are available in the registration dossier on the monomer. Data on a similar substance (Dapsone, CAS. No. 80-08-0) indicate increased photoinduced toxicity to bacteria under UV-B radiation, which might be due to toxic transformation products (Kawabata *et* al. 2013).

Phototransformation in soil

No data are available in the registration dossier.

7.7.1.2. Biodegradation

Biodegradation in water

Screening tests

A ready biodegradability test was conducted with BCPS according to a modified MITI Test (I), (NITE, 1999). After 28 days, 1% degradation measured as O_2 consumption was observed. Thus, BCPS is not readily biodegradable.

Simulation tests (water and sediments)

A reliable OECD 308 water / sediment simulation test is available with BCPS (Unpublished study report, 2014a). The biodegradation of radiolabelled BCPS was studied in two water/sediment systems (Tilft and Goose water/sediment systems, USA) under aerobic conditions.

The substance was dosed into the water at nominal rates of 0.37 and 0.30 µg a.i./g water for the Tilft and Goose River test systems, respectively. HPLC / UV / RAM analysis of the water layer throughout the study showed that the radioactivity was almost entirely BCPS as the radioactivity recovered in the water layer compared well with the %AR for BCPS. One significant peak (HPLC profile) in water and sediment was confirmed by GC/MS-EI analysis as BCPS.

The results for both water/sediment systems are presented in the tables below:

Table 9 %AR for Tilft Water / Sediment Systems

	% Applied Radioactivity (AR)						
	0 d	**7 d**	**14 d**	**30 d**	**50 d**	**75 d**	**100 d**
in Sediment							
extractable fraction	10.3	53.9	64.5	70.9	71.5	81.0	82.4
non-extractable fraction	0.5	1.4	1.2	2.2	2.4	3.5	4.4
$^{14}CO_2$	N/A	0.0	0.0	0.1	0.2	0.3	0.4
in water							
Total in water	91.9	45.6	34.8	27.0	22.4	16.3	12.7
Mass Balance	102.7	101.0	100.5	100.2	96.5	101.1	99.9

Table 10 %AR for Goose River Water / Sediment Systems

	% Applied Radioactivity						
	0 d	**7 d**	**14 d**	**30 d**	**50 d**	**75 d**	**100 d**
in Sediment							
extractable fraction	12.8	52.4	68.1	81.0	72.7	77.9	81.1
non-extractable fraction	0.3	6.2	6.9	15.5	13.7	17.4	15.2
$^{14}CO_2$	N/A	0.0	0.0	0.1	0.2	0.3	0.5
in water							
Total in water	87.2	38.6	22.9	9.9	7.5	3.8	2.6
Mass Balance	100.3	97.3	98.3	105.0	94.8	100.8	99.8

It can be concluded that degradation of BCPS was not observed in water or sediment. BCPS decreases from the water layer from above 88.8 and 85.1% AR at Day 0 to 12.4 and 2.4% AR at the end of the study. No degradation products were detected. CO_2 formation was negligible in both systems. In the sediment the concentration of BCPS steadily increased from more than 10.3 and 12.8% AR at Day 0 to 82.4 and 81.1% AR at Day 100. NERs increased over time in both systems (max. 15.2%). No degradation products ≥5% at two consecutive sampling intervals were observed.

DT_{50} values were calculated by the Registrants using ModelMaker® 4.0 and the results can be obtained from Table 11. BCPS dissipated from water into the sediment with a $DT_{50,diss}$ value of 7.1 and 6.2 days in the Tilft and Goose River system, respectively. Degradation in the whole system was not observed as the $DT_{50,deg}$ values were 1287.2 and 394.3 days in the Tilft and Goose water/sediment systems, respectively. The best visual fit and statistics for the data were obtained using the SFO model, whereas for the dissipation from the water using the DFOP model.

Table 11 Kinetics of parent compound BCPS

Water/Sediment Type	Layer	BCPS rate const. 1 (day -1)	BCPS rate const. 2 (day-1)	BCPS DT_{50} (days)	R^2
Tift (Sandy Loam)	Water	0.223	0.011	7.1	0.994
	Total System	0.001	N/A	1287.2*	0.31
Goose River (Clay)	Water	0.147	0.016	6.2	0.994
	Total System	0.002	N/A	394.3*	0.64

*extrapolation beyond the 100 day study duration

Summary and discussion of biodegradation in water and sediment

BCPS is not readily biodegradable and fulfils the criteria for "very persistent" in the sediment based on the OECD TG 308 study.

Biodegradation in soil

No data are available in the registration dossier.

7.7.2. Environmental distribution

7.7.3.1 Adsorption / desorption

The adsorption coefficient was determined according to OECD TG 121 (Unpublished study report, 2010). The log K_{OC} of 3.5 was interpolated with the HPLC method at 23°C and at pH 6.2 using several reference compounds. The results are considered reliable.

7.7.3.2 Potential for long range transport (LRTP)

Based on the vapour pressure and assuming BCPS is released to air, BCPS will exist in both the vapour and particulate phases in the ambient atmosphere (Norström *et* al., 2010) and the author further stated that BCPS may be removed from the atmosphere by wet and dry deposition. BCPS was measured in vapour and particulate phase (Norström *et* al, 2010). The atmospheric concentrations of measured BCPS were below the LOD (LOD < 2 pg/m^3) at Råo, Pallas and Stockholm (Norström *et* al, 2010). However, BCPS was detected in one air sample from the Swedish east coast (Aspvreten) in the same magnitude as individual PCB congeners (Norström *et* al. 2010), the concentrations were 8400 pg/m^3 in July 2009, 1500 pg/m^3 in November 2009 and 200 pg/m^3 in January 2010.

BCPS has a calculated DT_{50} in air of 27.3 days (24-hrs) or 54.7 days (12-hrs) indicating a potential for long range atmospheric transport (AOPWIN v1.92), therefore a model was used to estimate the LRTP. The OECD "Pov and LRTP Screening Tool"[9] has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of

[9] http://www.oecd.org/document/24/0,3343,en_2649_34379_45373336_1_1_1_1,00.html

PBTs/POPs assessments. The tool calculates metrics of (overall persistency) Pov and LRTP from a multimedia chemical fate model and provides a graphical presentation of the results.

The result for BCPS is plotted against the reference chemicals α-HCH, Aldrin, c-octaBDE, PeCB, BDE-99 and γ-HCH. The criteria lines were not modified and taken as proposed in the tool (Pov limit: 195 days, CTD limit: 5096 km, TE limit: 2.25 %) according to Klasmeier *et* al., 2006. CTD (characteristic travel distance) is a transport-oriented LRT indicator and quantifies the distance from the point of release to the point at which the concentration has dropped to 1/e or about 37% of its initial value. TE (transfer efficiency) is target oriented and focused on how much chemical reaches a certain distant target (Wegmann, 2009).

Following input parameters for Kow and Kaw, half-lives for water and soil were used and are listed in table 12. The input value DT50 water and soil are not derived from experimental findings; the calculated DT50 in air is > 2 days (AOPWIN v1.92).

Table 12 Half-lives for air, water and soil (input parameters for the OECD Tool)

Half-Lives	Value (h)	Source
Air	1330	AOPWIN v1.92
Water	1440	Level III Fugacity
Soil (DT50 lab)	2880	Level III Fugacity
Kaw	-5.252	KOAWIN v1.10
Kow	3.9	KOWWIN v1.10

The multimedia OECD model results indicate a similar potential of LRT than the reference chemical γ-HCH.

Input parameter of a DT_{50} of 54.6 days (12 hours) resulted in a calculated CTD (characteristic travel distance) for BCPS of 2071 km. The calculated TE value is 8.5 %. Pov is 170 days (ref. to Fig 1).

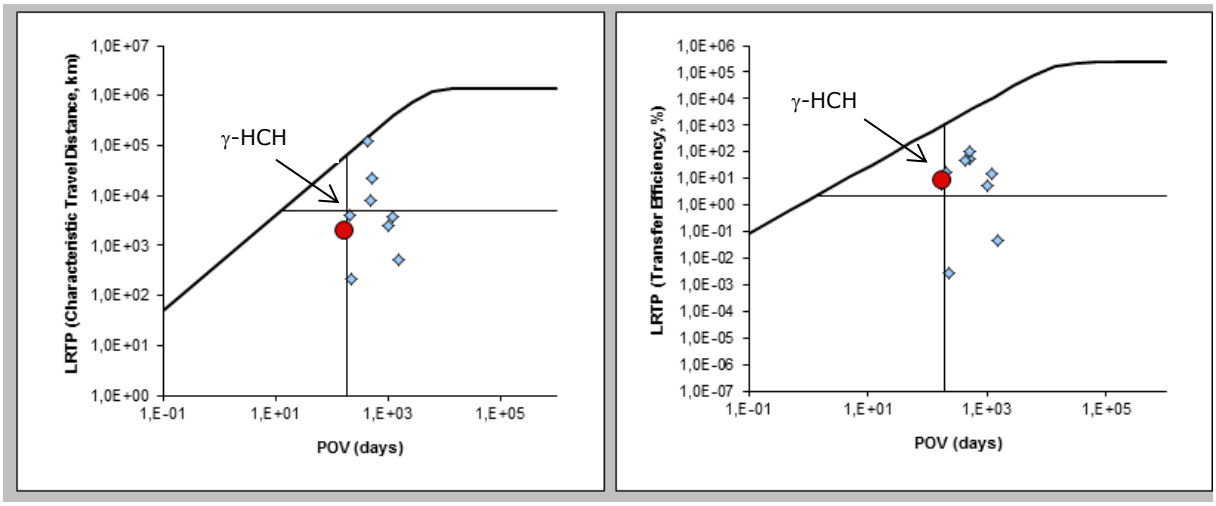


Figure 1: Results from the OECD Tool (CTD and TE) for BCPS (red point) and selected reference substances (α-HCH, Aldrin, c-octaBDE, PeCB, BDE-99 and γ-HCH).

Using the $DT50_{diss}$ of 7.1 days (from OECD TG 308) instead of the estimated DT_{50} for water, following results are obtained: P_{OV} = 168 days, CTD = 2066 km, TE = 8.4%, again BCPS is similar to γ-HCH.

According to Wegmann *et* al. 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT),

while substances of environmental concern are found in the upper right region (high Pov, high LRT).

However, no Monte Carlo Analysis for the given input parameter has been included in the calculation. Uncertainties concerning the input parameters, overestimation of photo-oxidative degradation in air (see Scheringer 2009[10]) as well as CTD and TE might not yield in all cases a relevant LRT description (see AMAP, 2009[11]). Monitoring data from very remote areas are summarized in chapter 7.7.5 Biotamonitoring.

7.7.3.3 Mobility of BCPS

The criterion for mobility (M) is based on a log K_{OC} value smaller than or equal to 4 (NGI, 2018). Based on the log K_{OC} of 3.5 (Unpublished study report, 2010a), BCPS fulfils the mobility criterion (M). Considering the screening criteria set out in the report of Crookes *et* al., 2018 for PMT (persistent, mobile, toxic) substances $logK_{OW} < 5$ or $logK_{OC} < 5$ with $logK_{aw} < -3$, BCPS[12] can be considered as mobile. BCPS falls into Mobile group 3, which indicates that the substance will tend to be transported mainly via water.

In conclusion, BCPS is considered as mobile and the main environmental transport might take place in water and not in air, nevertheless the ultimative sink of BCPS seems to be the sediment. Monitoring data in sediments are summarized in chapter 7.7.3.4

7.7.3.4 Measured levels in environmental compartments – field data

The conclusion on the modelling of distribution is further supported by monitoring, as BCPS is found in various aquatic environments.

Monitoring data come from analyses undertaken by the UK Environment Agency's National Laboratory Service. The data comprise of a large number of different sample points from across England. Data are compiled in Table 13. Targeted GC/MS screening for organic substances was carried out following sample pre-concentration. A double liquid-liquid extraction was employed, using acid-neutral dichloromethane, to extract non-polar substances. The GC/MS target based (multi-residue) screening method allows for over 850 substances to be identified from a single sample, including both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs). All of the results from this method should be treated with caution as they are from a semi-quantitative analysis method that is not accredited.

[10] http://onlinelibrary.wiley.com/doi/10.1897/08-324R.1/full

[12] BCPS: calculated $logK_{OW}$ (KOWWIN v. 1.67) = 3.9, calculated $logK_{OC}$ (MCI Method)= 3.5 and $logK_{aw}$ (Henry Win est) = -5.25, persistency > 1 year. The half-life from the total system in both water/sediment systems is > 1 year (1287 days for Tilft and 394 days for the Goose River, (Unpublished study report, 2014a)).

Table 13 Semi-quantitative GC/MS target based screen data for 4,4'-dichlorophenyl sulfone (CAS Number 80-07-9)

Media	Year	Country	No. of positive detections	Approximate minimum concentration µg/L	Approximate maximum concentration µg/L	Approximate detection frequency	Limit of detection
Surface water	2012 - 2017	England, UK	59	0.004	0.4	0.4%	Not evaluated
Ground-water	2012 - 2017	England, UK	11	0.007	0.3	0.1%	Not evaluated
Estuarine /coastal water	2012 - 2017	England, UK	46	0.003	0.32	1.1%	Not evaluated
Landfill leachate	2012 - 2016	England, UK	2	0.01	1	1.1%	Not evaluated

Method: Targeted GC/MS screening for organic substances was carried out following sample pre-concentration. A double liquid-liquid extraction was employed, using acid-neutral dichloromethane, to extract non-polar substances. The GC/MS target based (multi-residue) screening method allows for over 850 substances to be identified from a single sample, including both volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs).

Semi-quantitative data: All of the results from this method should be treated with caution as they are from a semi-quantitative analysis method that is not accredited.

Sample points: The data come from a large number of different sample points from across England.

Distribution of the concentrations: Max and min concentrations are presented in the table. The data are typically skewed towards the minimum concentration with most values being below 0.05 µg/L.

Potential source: Analysis of groundwater quality data (ref. Table 13) suggests that a possible source of this chemical could be plastic pipe fittings at the groundwater abstraction. These fittings may be leaching 4,4'-dichlorophenyl sulfone into the water as the groundwater sample is being taken. This potential source has not been confirmed.

Effluents from Wastewater treatment plants (WWTPs)

Norström *et* al., 2010 investigated several sources among different effluents from WWTPs sampled from Poland, Sweden, Finland, Estonia and Lithuania. Only in one WWTP, the effluent from WWTP2 located in Estonia 17 ng/L BCPS were detected in 2009 (LOD < 8 ng(L). Recently, BCPS was detected in effluents from WWTPs (Zilina, Budapest, Ljublijana, Sabac, Zagreb) at concentrations 0.4 – 11.8 ng/L (Project: ITN, Answer, Solutions).
Samples were taken between 15th of August 2017 – 1 Sept. 2017, more information on sampling locations is available under:
https://www.sciencedirect.com/science/article/pii/S0160412019304052

Surface water

Germany

BCPS has been detected in water samples in Germany (cited *in* Norström *et* al. 2010, originally from Müller *et* al., 1997).

Marine Surface Water

Sweden

In 2010, surface samples were analysed (Norström *et* al., 2010). The surface water sampled in Råö, Sweden contained 0.45 ng/L. The surface water concentration in Silviken, Ljusterö, Sweden revealed 1.3 ng/L and in Riddarfijärden, Sweden 0.33 ng/L BCPS, respectively.

Black Sea

BCPS was detected in 20 out of 24 samples collected in the Black Sea in 2016 (EMLAS-II project) and in seawater samples from five stretches of the Black Sea during the campaign that took place in 2017.

Danube Delta

Additionally, BCPS was detected in sediment and water samples collected from the Danube delta. Concentration levels ranged from 1.4 to 3.1 ng/L in seawater and from 8.1 to 14 ng/g in sediment (projects: Seawater and sediment from Black Sea Survey 2017).

Drinking water

USA

BCPS has been summarized in a Swedish report[13] (Norström *et* al., 2010), where it was stated that BCPS was detected in drinking water in USA (Lucas *et* al., 1984).

Sediment

Norström *et* al., 2010 analysed BCPS in sediment samples from the North Sea (SE15), Baltic Sea (n=2; Gotland basin) and Långholmen, Sweden. The concentrations were below < 4 ng/d.w.

7.7.4. Bioaccumulation

7.7.4.1 Bioaccumulation in aquatic organisms (pelagic and sediment organisms)

Screening data

Log K_{ow}

Estimated log K_{ow}

For the PBT and vPvB assessment a screening criterion has been established, which is Log K_{ow} greater than 4.5. The substance does not screen as pot. B/vB based on the predicted Log K_{OW} of 3.9 (EPI Suite, EPI Web 4.1, KOWWIN v1.68). The used model is expected to be applicable for BCPS and the predictions to be valid.

Measured log K_{ow}

The shake flask method (OECD TG 107) was used and low K_{OW} of BCPS was determined to be 3.9 at 20°C (Unpublished study report, 2006a).

Estimated BCFs for BCPS

The eMSCA estimated the BCFs using the BCFBAF program (BCFBAF v3.01) within US EPA EPI Suite v4.11 using the following smiles code for BCPS

[13] http://www.utslappshandel.se/Documents/publikationer/620-6164-X.pdf

ClC1=CC=C(C=C1)S(=O)(=O)C1=CC=C(Cl)C=C1. The predictions have been carried out with the estimated log K_{OW} of 3.9 (KOWWIN v.1.68). Estimated BCF values indicate a low bioaccumulation potential in fish (see below). The used model is expected to be applicable for BCPS and the predictions to be valid.

Table 14 Estimated BCFs for Bis (4-chlorophenyl) sulphone (CAS 80-07-9)

Bioaccumulation Estimates (BCFBAF v3.01)		
BCF (regression based method)	**BCF Arnot-Gobas Method (upper trophic)**	**BAF Arnot-Gobas**
172.8	675	692.3

The Registrants predicted BCF and BAF values with US EPA EPI Suite (ver. 4.1) BCFBAF v3.01 ($BCF_{Arnot\text{-}Gobas,\ 5\%Lipid}$ normalized = 309.8; BAF $BCF_{Arnot\text{-}Gobas,\ 5\%Lipid}$ normalized = 318) and the QSAR program CATALOGIC BCF LMC, Laboratory of Mathematical Chemistry, v. 02.09 -July 2017) predicted for BCPS a BCF of 269 L/kg wet weight at steady-state (Vertellus, 2018, personal communication) .

Calculated BCF values are < 2000, indicating a low potential for aquatic bioaccumulation.

Experimental BCF data for BCPS

One experimental study on the aquatic bioaccumulation in carp is available (NITE, 2001). The study was performed with non-radiolabeled BCPS and without a depuration phase, therefore no depuration rate constant and no kinetic BCF is available. In OECD TG 305 it is defined, when a steady-state has been reached. In the BCF study, the duration of exposure was 35 days and has been prolonged as no steady-state could be reached after 28 days. Steady-state was assumed to be reached during the exposure phase. Authors stated that the variation in the bioconcentration factors (mean) after 21, 28 and 35 days were within 20% of the mean value for bioconcentration factor in these 3 analyses. Therefore the authors judged that a steady-state had been reached. No BCPS concentration in fish data is available in the translated report. Consequently, the steady-state can not be assessed by the eMSCA. The Japanese version cannot be retrieved from the NITE page and is also not fully available to the eMSCA. Nevertheless, the substance was stable under the test conditions. No fish abnormalities were observed.

Table 15 BCF data for BCPS

Method	**Results**	**General comments on method**	**Reference**	**Validity/Comments**
Cyprinus carpio Yearling fish Body length: 6.9 – 8.1 cm aqueous (freshwater) flow-through uptake phase: 35 d	BCF: 75L/kg (whole body weight) BCF: 82L/kg (whole body weight) Normalized to 5% lipid	Test material name: "K-1200" bis(4-chlorophenyl) sulphone Two conc. used: 5 µg/L 50 µg/L well below water solubility of 0.832 mg/L, at 20°C	NITE, 2001 National Institute of technology and evaluation (Japan)	Registrant(s) ranked the study as Klimisch 2 (reliable with restrictions). Limitations: Report is not fully available to eMSCA, as original data are missing e.g. conc. of BCPS in fish. No depuration phase has been conducted, no lipid normalized BCFss are available, test item was not radio-

Method	Results	General comments on method	Reference	Validity/Comments
depuration time: 0 d Based on Bioconcentration test of chemicals in fish and shellfish (Kanpogyo No. 5, Yakuhatsu No. 615, 49 Kikyoku No. 392)	content by eMS: 187.5 L/kg 205 L/kg	Fish lipid content 2% (at start and end of exposure) Dispersant: HCO-40		labelled. Results cannot be fully judged by the eMSCA. In the OECD guideline 305 it is stated that "a depuration phase is always necessary, unless uptake of the substance during the uptake phase has been insignificant."

7.7.4.5 Bioaccumulation in terrestrial organisms

Screening

Screening criteria[14] for air-breathing organisms have been established and are based on Log K_{OW} > 2 and Log K_{OA} > 5.

The measured log K_{OW} is 3.9 (Unpublished study report, 2006a) and the estimated log K_{OA} value of 9.2 (KOAWIN v.1.10), indicating a bioaccumulation potential in terrestrial organisms. The used model is expected to be applicable for BCPS and the predictions to be valid.

The substance belongs to polar non-volatiles, which do not biomagnify in aquatic organisms, but may substantially biomagnify in air-breathing (terrestrial) organisms. BCPS has been mentioned as an example for a hydrophilic compound to exhibit a bioaccumulation potential (Kelly *et* al., 2004).

Toxicokinetic data for bis (4-chlorophenyl) sulphone

Toxicokinetic studies (e.g. according to OECD TG 417) provide further information on the bioaccumulation potential of a substance. Toxicokinetics studies (summarised in section 7.9.1) demonstrate that BCPS is readily absorbed and distributed fast from blood into tissues, mainly to lipid-rich tissues such as adipose.

After intravenous administration of 10 mg/kg increasing accumulation of BCPS in adipose tissue was observed up to 24 hr, followed by slow elimination. A terminal half-life (rat, i.v. application) in adipose tissue of 12 days has been estimated. The study author concludes that based on these observations BCPS has the potential to bioaccumulate in the tissues of higher animals and in the environment if exposure occurs.

However, in the same publication in a five week repeated dose (10 mg/kg bw/day) study tissue concentrations (e.g. from 19,6% dose in total tissue week 1 to 6.72% dose in total tissue week 5), which indicates accelerated clearance from tissues after repeated dose. This observation might be hampered by the influence of the vehicle (Elmuphor EL 620) used on metabolising enzymes (as highlighted in NTP, 2001). Elmuphor itself doubles CYP450 content. Liver enzyme induction was significantly increased compared to vehicle control at a dose level of 10 mg/kg bw and no alteration was found at a dose of 1 mg/kg bw (7 days exposure), indicating that enzyme induction is dose dependent.

[14] https://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf

Furthermore, this time-dependent decrease in content of BCPS in tissue after repeated dosing was not substantiated in a further repeat dose (75.6 mg/kg bw/day for 28 days, diet, vehicle: corn oil) rat study, in which the content of BCPS remained unchanged between week 1 and 4, and even increased in kidneys.

The excretion of BPCS depends on metabolism to more polar compounds, thus the BCPS levels found in sample material might be influenced by the induction of phase I and phase II enzymes present in the respective individual or wildlife species exposed.

It has been demonstrated that BCPS can induce phase I and phase II enzymes (e.g. CYP450 enzymes, UDPGT and GST) in the aforementioned toxicokinetic studies.

Mathews et al. (1999) concludes that BCPS might induce CYP1A forms but not CYP2B forms, whereas Ponn et al. (1996) observed an induction in CYP2B related markers. More data or information on the influence of BCPS on different CYP450 isoforms would be of interest to further characterise enzymatic metabolism attributable to BCPS among different species.

Biota/Biotamonitoring

BCPS was monitored in different wildlife species over various trophic levels from fish in fresh and sea water, up to top predators (e.g. grey seals, fish-eating birds, mink, otters, buzzards). Monitoring data are sorted according to different taxonomic groups (fish, seals and birds, other organisms) and humans (ref. annex section 7.17).

Biota/biomonitoring in fish

Analyses of BCPS in various fish species from different countries (Latvia, Lithuania, Poland, Estonia, Germany, Sweden, Austria, Georgia, and Ukraine) revealed that BCPS is detected above Limit of Detection (LOD) in fresh and marine fish samples (e.g. Norström *et* al., 2004, Norström *et* al., 2006; Norström *et* al., 2010; Olsson *et* al., 1999; and Valters *et* al., 1999; Hornek-Gausterer *et* al., 2020, Black Sea: project JBSS, 2017), except for one very remote region.

The highest fish BCPS values are found in the Baltic Sea, which is among the most polluted water bodies in the world. It is a semi-enclosed water body having limited water exchange to the North Sea. Increasing BCPS trends have been observed by Norström *et* al., 2004 in salmon from the Baltic Sea and in Artic char obtained from an oligotrophic lake in Sweden. In Lativia, from 1997 to 2008, the BCPS level in perch was at one location (Daugava) within the same range, from 38 to 48 ng/g l.w. (K. Norström *et* al., 2010; Valters *et* al., 1999). A more or less same stable concentration over 10 years was observed in herring, which was around 30 ng/g l.w. from different locations in Sweden, Poland and Lithuania (Norström et al., 2004 and 2010). BCPS was detected in five fish samples from the Black Sea, one from Ukraine and four from Georgia (Black Sea: project JBSS, 2017). The concentration levels in fish samples ranged from 0.9 to 2.2 ng/g wet weight. Fat content was not measured, but assuming a fat content of around 5% this would yield a BCPS concentration of 18 – 44 ng/g l.w.. Recent data from fresh water fish (Danube, Austria) show max. BCPS level of 9.1 ng/g fat (Hornek-Gausterer *et* al., 2020).

Nevertheless, local industrial input sources might be responsible for the different BCPS concentrations measured. The distribution pattern of BCPS is obviously different from other organochlorine pollutants, as shown by measurements of muscle tissue from fish of 4,4´-DDE and CB-153 (Norström *et* al., 2004). DDT was banned in Latvia in 1966, so since then no new input of BCPS as impurity should have taken place (Olson *et* al., 1966). Recent monitoring from 2019 shows, that DDT (incl. metabolites) in contrast to BCPS could not be detected in any Austrian freshwater fish samples (Hornek-Gausterer *et* al., 2020).

Biotamonitoring - Birds

Most of the investigated samples (eggs, breast muscles, liver, plasma) from birds (*Haliaeetus albicilla*, *Uria aalgae*, *Rynchops niger, Phalacrocorax carbo carbo, Larus hyperboreus*) detected BCPS showing widespread bioavailalbility in birds from different regions (Sweden; California USA; Iceland; Faroe Islands; Norway; Austria) including the Norwegian arctic (e.g. Olsson, 1995; Letcher et al. 2005; Helander *et* al., 2002, Verrault *et* al., 2005; Jörundsdóttir *et* al., 2006 and Jörundsdóttir *et* al. 2008; Norström *et* al., 2004; K. Norström PHD thesis, 2006; Millow *et* al., 2015; (Hornek-Gausterer *et* al., 2020).

In the time period 1971 – 1991, BCPS was detected from a non detectable level up to highest values of 610 ng/g in the eggs of white tail sea eagle (Helander *et* al., 2002). In detail, in the years from 1971-76 BCPS ranged from n.d. to very low conc. of 16 ng/g. From 1987-91, BCPS was detected in all eggs with mean conc. of 170 and 110 ng/g.

From all biota samples so far analysed the BCPS levels detected were highest in Guillemont eggs from the island Störa Karlsö, Sweden (760 - 2600 ng/g l.w., mean: 1136, period: 1971 - 2003). BCPS was found in an at least constant trend in eggs from 1971 to 2003 (Jörundsdóttir *et* al., 2006 and Jörundsdóttir *et* al., 2008). Grey seals feed on herring like Guillemot, but the difference in BCPS levels might be explained by differences in the elimination capacity in birds and mammals (Jörundsdóttir *et* al., 2006).

In a recent study from 2019 (Hornek-Gausterer *et* al., 2020) eleven Cormorants were investigated for the level of BCPS, five individuals from 2001 – 2005 (breast muscle), and six individuals from 2019 (breast muscle and liver). Level found were in all cases above LOD. These data from breast muscle BCPS levels in Cormorants (*Phalacrocorax carbo carbo*) in Austria show, that the concentration in 2019 is lower (4.3 – 40 ng/g fat, mean: 16 ng/g fat, n=6) compared to the breast muscle concentration from Guillemot obtained in the BCPS area in Sweden, Störa Kalsö (up to 1900 ng/g l.w.; Norström et al., 2004), but underpin the results from Guillemot eggs from Jörundsdóttir *et* al., 2006 and Jörundsdóttir *et* al., 2008 in the sense, that although the sample size of the Cormorants was small, no decreasing trend in the BCPS level was obtained. The results showed an increasing trend in Cormorant´s breast muscle from 8.9 (2001- 2005) to 16 ng/g fat (2019) nevertheless the number of samples is rather low. Depending on the weather and local wintering conditions cormorants may stay in Austria or will move onward using all kind of open surface water bodies as wintering grounds along their migration route (e.g. van Eerden *et* al. 2011). The individual´s migration route is unknown and food could have been taken up along the way. Even if these cormorants had ingested fish from the Baltic region, where the former concentration of BCPS was shown to be around ~ 30 ng/g l.w. in fish (the southern Baltic[15]), the BCPS concentration in liver (mean: 53.5 ng/g fat, n=6) is still higher than the mean BCPS concentration in fish. In that study, the mean BCPS concentration in sub-adult cormorants was 8.85 ng/g fat and the concentration in adults revealed mean BCPS concentrations of 17.7 ng/g fat, indicating an increase in BCPS concentration in breast muscle with age and accumulation over life time. But due to the low sample size and as the results are not statistically significant, no final statement was made (Hornek-Gausterer *et* al., 2020).

Biotamonitoring - Grey seals

Grey seals are in general highly contaminated due to their food and their long life. Grey seals are present mainly in the north and centre of the Swedish east coast. Grey seals feed mostly on fish. Liver, lung and blubber from Swedish grey seals were investigated for the

[15] In Landsort, Sweden the concentration was 29 – 31 ng/g l.w. in 1998 and at the Souther Baltic Coast, Kvädöfjärden, Sweden the BCPS concentration was 35 (n=5) and 37 (n=5) in 1998, the concentration in herring (1998) was 33 ng/g l.w. (K. Norström *et* al., 2010). The concentration in Salmon in Gotland, Sweden was 31 and 33 ng/g l.w. (Norström et al., 2004). In 2008, the concentration in herring in the Gulf of Dansk, Poland was 32 ng/g l.w. and the coastal area north from Klaipeda, Lithuania revealed in 2008 26 ng/g l.w. in herring (Norström et al., 2010).

presence of BCPS (e.g. Olsson and Bergmann, 1995; Larson *et* al., 2004; Norström *et* al., 2004). In the study from Larson *et* al., 2004, the BCPS levels in blubber, lung and liver (2000-01) from the Northern Baltic Sea in Sweden were compared. The highest BCPS concentration was found in the liver of grey seals (median: 200 ng/g l.w.; range 55 – 700 ng/g l.w.; n=10). The concentration in the blubber was lower than in liver, which was in the range of 41 – 240 ng/g l.w. (median: 60 ng/g l.w.; n=10). The health status of seals seemed to affect the BCPS levels detected in the blubber of seals, as shown for an unhealthy individual where the blubber concentration was higher (480 ng/g l.w.) compared to healthy individuals (range: 49 – 98 ng/g l.w.; Norström *et* al., 2004). Details on the effects were not mentioned in the publication.

Biotamonitoring - other organism

1. **Screening programme 2017 (2018):**

Detection frequency is given by the number of detections divided by the total number of measured samples given in percent. Detection frequency for BCPS was 20% in Arctic mink (n= 5) and 20% in Common gulls (n=5) in Hot Spots/urban area. The concentration of BCPS in mink was 0.5 ng/g w.w. and in Common gull 0.2 ng/g w.w.

2. **Top predators and their prey from LIFE APEX project[16]**

BCPS was detected in liver of top predators (otters) in levels from 1.1 – 7.2 ng/g wet weight (c.f Table 16).

Table 16 BCPS concentration in various biotas

Sample description	BCPS concentration (ng/g wet weight)	Country
Bream muscle from Rhine Bimmen	2.8	Germany
Eelpout muscle from Baltic Sea, Darßer Ort	< 0.9 (LOQ=0.9)	Germany
Otter liver from North Wales	< 0.9 (LOQ=0.9)	United Kingdom
Otter liver from Overjissel	5.2	Netherlands
Otter liver from Groningen	1.1	Netherlands
Otter liver from Harich, Friesland province	7.2	Netherlands
Bream muscle pooled from Zuid - Holland	< 0.9 (LOQ=0.9)	Netherlands
Buzzard liver pooled from Mecklenburg Vorpommern	< 0.9 (LOQ=0.9)	Germany
Otter liver pooled from Västmanland/Örebro	< 0.9 (LOQ=0.9)	Sweden
Otter liver from Plön	1.2	Germany
Otter liver from Bösdorf	5.3	Germany

[16] https://lifeapex.eu/

Biotamonitoring – humans

Table 17 Human biomonitoring data

Method	Results	Remark	Reference
Six human liver and lung samples (3 males, 3 females) Analysis of MeSO2-PCBs, 3-MeSO2-DDE and BCPS GC/MS	BCPS was found in all liver samples, not in lung samples	Authors noted that both laboratories involved encountered considerable background level of BCPS. Thus, special caution has been applied to verify the content of BCPS (blank, standard compound).	Ellerichmann T et al. (1998)
Development of screening methods in biological samples (human blood and urine) Analysis of human blood and urine samples (n=8) GC/MS	BCPS has not been identified in human blood. Several substances could be (tentatively) identified, among these were UV-filters like benzophenone-3 and several benzophenone metabolites, organophosphate flame retardants like triethylphosphate, 4-hydroxy-chlorothalonil and a bromo-quinolinole.	Screening study in which BCPS has been included in the screening list of contaminants in human blood (not in urine). BCPS is rapidly distributed from blood into lipid rich tissues.	Plaßmann et al. (2016)

BCPS was detected in human liver samples (Ellerichmann et al., 1998), in which also two types of $MeSO_2$-polychorinated biphenyls (PCBs) and $MeSO_2$ – Dichlordiphenyldichlorethen (DEE) were found. A quantification of the BCPS content has not been carried out, however, data indicate that the BCPS peak was about five times higher compared to $MeSO_2$-PCBs. Authors noted that both laboratories involved encountered considerable background level of BCPS. Thus, special caution has been applied to verify the content of BCPS (blank, standard compound).

In a non-target screening analysis BCPS was not found in human blood samples (lowest detectable concentration 2 ng/ml, which is in concordance with a rat toxicokinetic study of Mathews et al. (1999) demonstrating that BCPS levels in blood are low and that substance is distributed into tissues.

It is stated in the PhD thesis of K. Norström, that in the study where Me-SO2-PCBs in human serum was determined in PCBs contaminated areas in Slovakia (Hovander *et* al., 2006) BCPS was detected as significant contaminant in participants' blood (personal communication with Lotta Hovander). These data are however not published.

There is some evidence that BCPS is also detected in humans, but by far too few human data are present to draw a conclusion.

7.7.5. Summary and discussion of bioaccumulation

In this chapter, the data from the previous chapter were used to come to a final conclusion on bioaccumulation. Based on all lines of evidence, and despite the uncertainties of monitoring data, sample size and limited other air-breathing organisms, eMSCA concludes that BCPS is vB.

Aquatic bioaccumulation

- The screening criteria for bioaccumulation for aquatic organisms based on log K_{ow} > 4.5 is not fulfilled based on measured and predicted values.

- Calculated BCF values < 2000 (US EPA EPI Suite (ver. 4.1), BCFBAF v3.01) indicate a low potential for aquatic bioaccumulation. The measured lipid normalized BCF is 205, the study revealed some limitations (NITE, 2001).

Biomagnification

- Field BMF values (fish, bird) > 1

  A BMF value significantly higher than 1 can be considered as an indication for very high bioaccumulation.

  Fish, Guillemot: The concentrations of BCPS in herring between 1998 and 2008 were in the range between 17 – 58 ng/g l.w., concentration seems to stay at a constant level of around 30 ng/g l.w. in herring obtained from Sweden, Poland and Lithuania (Norström *et* al., 2004 and 2010). The concentration in herring 1996 was between 31-33 ng/g l.w (Norström *et* al., 2004, Sweden). There was no obvious trend between country or sampling location (Norström *et* al., 2010). Therefore it seems reasonable to take the fish muscle BCPS level of around 30 ng/g l.w. and to compare it with the concentrations found in Guillemot breast muscle 1600 ng/g and 1900 ng/g (1998) from the Baltic region (Norström *et* al., 2004). Guillemots feed stationary on herring and sprat. Unfortunately, no recent data are available from this region. Since BCPS biomagnifies among food chains, the concentration of BCPS increases as the trophic level increases. When calculating a field BMF values, the concentration in the predator is divided by the concentration in the prey, which results in field BMF values of 53 to 63 for herring and Guillemot.

  Fish, Cormorants: The BCPS concentration was higher in fish-eating birds (breast muscle mean: 16.3 ng/g fat, n=6) than in fish (mean: 4.9 ng/g fat, n = 6), which indicates that BCPS biomagnifies. A biomagnification factor (BMF) is the ratio of the concentration in the predator divided by the concentration in the prey, in this case the field $BMF_{cormorant\ breast\ muscle,\ whole\ fish}$ values is 2.96, which is significantly higher than 1 and can therefore be considered as an indication for very high bioaccumulation (ECHA, 2017). One cormorant had ingested fish, with a BCPS level of 5.5 ng/g fat, the BCPS level in the cormorant breast muscle was 23 ng/g fat, suggesting a BMF of 4.2.

- Field BMF values (herring, seals) > 1

  A BMF value significantly higher than 1 can be considered as an indication for very high bioaccumulation.

  Fish, Grey Seals: The concentrations of BCPS in herring between 1998 and 2008 were in the range between 17 – 58 ng/g l.w., concentration stays in herring at a certain level of around 30 ng/g l.w. obtained from Sweden, Poland and Lithuania

(Norström *et* al., 2004 and 2010). It is therefore reasonable to take the fish level of around 30 ng/g l.w. and to compare it with the concentrations found in liver and blubber from grey seals (liver: 200 ng/g and blubber: 60 ng/g) from the Baltic region. This biomagnification potential can be expressed by a biomagnification factor (BMF). When calculating a field BMF values, the concentration in the predator is divided by the concentration in the prey, which results in field $BMF_{herring, seals\ liver}$ values of 6 to $BMF_{herring, seals\ blubber}$ of 2.

Field data

Several field studies measuring the concentration of BCPS are available from 1971 – 2019 (ref. annex section 7.17). There is evidence, that BCPS was taken up and detected above Limit of Detection (LOD) in different wildlife species (marine and freshwater fish, grey-seals, birds, mink, otters) throughout aquatic food chains, including top predatory fish, as well as grey seals *Halichoerus grypus* and fish-eating birds (like e.g. white tailed-sea eagle, guillemot, cormorants). Data were mostly generated for the Baltic region, but also include remote areas (Arctic) and data from North America, Austria, Black Sea and Danube delta.

- Highest BCPS levels constant over 30 years were detected in fish-eating bird eggs (high trophic level)

  From all biota samples analysed so far the BCPS levels detected were highest in Guillemont eggs from the island Störa Karlsö, Sweden (760 - 2600 ng/g l.w., mean: 1136 ng/g l.w., period: 1971 - 2003). BCPS was found in an at least constant level in eggs of the fish-feeding bird, Guillemot from 1971 to 2003 (Jörundsdóttir *et* al., 2006 and Jörundsdóttir *et* al., 2008).

- High BCPS levels in seals

  The highest BCPS value (=480 ng/g l.w.) was found in grey seal blubber in an unhealthy 11-year old individual (Norström et al., 2004). Larsen *et* al., 2004 investigated lung, liver and blubber from grey seals from Sweden. The target organ of BCPS is the liver, exhibiting the highest concentrations (median = 200 ng/g l.w.; range 55 – 700 ng/g l.w., n=10). The concentrations in the blubber was lower than in liver, which was in the range of 41 – 240 ng/g l.w (median 60 ng/g l.w., n=10).

- Constant levels of BCPS in fish (perch, herring) over at least 10 years

  Perch: In Lativia, from 1997 to 2008, the BCPS level was at one location (Daugava, Latvia) within the same range, between 1997 and 2008, values were in the range of 38 – 48 ng/g l.w. (K. Norström *et* al., 2010; Valters *et* al., 1999). Again, a more or less same stable concentration over 10 years was observed in herring, which was around 30 ng/g l.w. from Sweden, Poland and Lithuania.

  Herring: BCPS concentrations in herring were quite stable over 10 years (Norström *et* al., 2010), taking the fish levels from 2008 (Sweden: 17 and 58 ng/g l.w.). The concentrations of BCPS in herring between 1998 and 2008 were in the range between 17 – 58 ng/g l.w., concentration stays in herring at a certain level of around 30 ng/g l.w. obtained from Sweden, Poland and Lithuania (Norström *et* al., 2004 and 2010).

- Recent data (Hornek-Gausterer *et* al., 2020)

  In predatory fish species (2019, Austria, Danube, N=8) and cormorant samples (2019, Austria, samples from liver and breast muscle) BCPS was detected. In all cases BCPS was detected above LOD. Levels in freshwater fish ranged between 1.3 and 9.3 ng/g fat. BCPS levels in cormorants breast muscle were in the range of 4.3 to 40 ng/g fat (mean: 16.3 ng/g fat, n=6) and 28 to 86 ng/g fat (mean: 53.5 ng/g fat, n=6) in the liver samples. The obtained concentrations are much lower than

compared to breast muscle concentrations from Swedish Guillemot (1600 – 1900 ng/g l.w.; Norström *et* al., 2004). But comparing the BCPS concentrations of cormorants' breast muscle from 2019 (mean: 16 ng/g fat, n=6) to the concentrations from 2001 – 2005 (mean: 8.9 ng/g fat, n=5), indicates that BCPS level is increasing, despite the small sample size and unknown food intake during the migration route of the individuals. Further, the mean BCPS concentration in sub-adult cormorants was 8.85 ng/g fat and the concentration in adults revealed mean BCPS concentrations of 17.7 ng/g fat, indicating an increase in BCPS concentration in breast muscle with age. But due to the low sample size and as the results are not statistically significant, no final statement can be made.

Increasing BCPS trend in fish and birds

The highest fish BCPS values are found in the Baltic Sea, which is among the most polluted water bodies in the world. Increasing BCPS trends have been oberserved by Norström *et* al., 2004 in salmon from the Baltic Sea and in Arctic char obtained from an oligotrophic lake.

In the study from Helander *et* al., 2002, BCPS was detected from a non detectable level up to highest values of 610 ng/g l.w. in the eggs. In detail, in the years from 1971-76 BCPS ranged from n.d. to very low concentrations of 16 ng/g. From 1987-91 BCPS was detected in all eggs with mean conc. of 170 and 110 ng/g.

Although the sample size was rather small, mean values of BCPS in cormorant muscles (Hornek-Gausterer *et* al., 2020), the results obtained so far showed an increasing trend from 8.9 (2001- 2005) to 16 ng/g fat (2019).

Terrestrial bioaccumulation

- Screening criteria for terrestrial bioaccumulation are fulfilled

  The measured log K_{OW} of 3.9 (Unpublished study report, 2006) and the estimated log K_{OA} value of 9.2 (KOAWIN v.1.10) indicate a bioaccumulation potential for terrestrial organisms. Kelly *et* al., 2004 mentioned BCPS as an example for a hydrophilic compound to exhibit bioaccumulation potential.

- BCPS exhibits a very long half-life in rats and has a high affinity to adipose tissue

  A very long terminal half-life was observed in adipose tissue of 12 days in rats after single i.v. application (cf. Chapter 7.9.1). BCPS is mainly distributed to adipose tissue and the affinity to adipose tissue is high. Accelaterated clearance was observed after repeated dosing and a steady state was observed after 2-3 weeks indicating a shorter half life (~ 5 days) after repeated dosing. This observation can be attributed to altered mechanism in rats after repeated exposure attributable to liver enzyme induction. The liver metabolism might vary between species, e.g. it is known that the half-lifes for polychlorinated biphenyls are in rats much shorter than in humans mostly due to higher metabolism rate in rats.

  BCPS detected in human liver

  BCPS has been detected in human liver samples (Ellerichmann *et* al., 1998)

- Different metabolism birds versus mammals

  BCPS, as a sulphone containing chemical has been detected in grey seals together with other sulphone containing substances 3-Me-SO_2-DDE, MeSO_2-PCBs to exhibit a high selective retention in the liver (Larsson *et* al., 2004). Recent data from cormorants show that the BCPS concentrations in liver were 1.2 – 17. 9- fold higher (mean: 6.7) than in breast muscle tissue, except for one individual with a liver to

breast muscle ration of 0.9 (Hornek-Gausterer *et* al., 2020). Birds and mammals have significantly different metabolism of xenobiotic. One of these differences is shown by the high concentration of BCPS in guillemots compared to grey seals in the Baltic region, despite the same food intake (Norström *et* al., 2004). Jörundsdóttir *et* al. 2006 indicated that birds are less capable of metabolising para-halogen substituted phenyl rings. The number of isoforms of CYPs might also differ between bird species.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

For fish (*Brachydanio rerio*) an OECD Guideline 203 limit study from 2006 is available showing no toxicity at 0.98 mg/L based on mean measured concentrations (Unpublished study report, 2006b).

No chronic fish toxicity data are available, although there are indications for endocrine disruption – particularly regarding an antiandrogenic mode of action from available in vitro data.

7.8.1.2. Aquatic invertebrates

No experimental data on acute toxicity are available. QSAR (ECOSAR v1.11) predict a 48-hr LC_{50} of 3.14 mg/L for Neutral Organics including a flag that the substance may not be soluble enough to measure this predicted effect.

For chronic toxicity a 21d-NOEC of 0.32 mg/L (reproduction) based on mean measured concentrations was identified in an OECD Guideline 211 with *Daphnia magna* (Unpublished study report, 2004a).

7.8.1.3. Algae and aquatic plants

In an OECD Guideline 201 with *Selenastrum capricornutum* the 72-h EC_{50} for growth rate and biomass was > 0.8 mg/L, the 72-h NOEC for growth rate and biomass was 0.28 mg/L based on mean measured concentrations (Unpublished study report, 2004b).

7.8.1.4. Sediment organisms

According to OECD TG 218 study with *Chironomus riparius* a NOEC of 11.8 mg/kg sediment dw tot (Unpublished study report, 2014b) a NOEC of 11.8 mg/kg dw based on both survival and emergence rate was reported. The most sensitive endpoint was emergence rate with an EC_{50} value of 40.5 mg/kg dw. The reported values for the development rate endpoints were notably higher.

7.8.2. Terrestrial compartment

Misra *et* al., 1957 investigated the insecticidal activity of various compounds (sulphones, cyanoethylated sulphones, sulphonamides, DDT, and Pyrethrum) under similar conditions (against fly *Musca nebulo*). The test was performed according to the method published in Misra *et* al., 1956, which includes also spraying of the solvent onto flies (resulting in no observed mortality). 20 flies/test were used in a closed chamber and a stock solution (Testbenzin/BCPS) was prepared (1 g/100cm^3 , Testbenzin) and 0.2 cm^3 were sprayed on the flies. 2 mg BCPS were applied on 20 flies, assuming an evenly spraying leading to the knock down rates summarized below at the conc. of 0.1mg/fly. The test is used to compare the efficacy of different tested compounds against flies. It is a phase 2, step 1 test as it is sprayed on the flies, but the uptake itself was not investigated.

Table 18 Summarised results

Substance	Conditions during Testing		Knock down in minutes	
	Temperature	rel. Humidity	50%	100%
BCPS (p,p´-Dichlordiphenyl-sulphone)	30.5	67	1.0	2.5
p-chlorodiphenyl-sulphone	31	67	20% up to 2 hours	
DDT	30	83	3	5

(adapted from Misra *et*. al., 1957)

P-chlordiphenylsulphone is not active, but the introduction of another chlorine atom in the second benzene ring enhances (BCPS) the activity. Insecticidal activity of BCPS is better than that of DDT, at least against fly *Musca nebulo* (Misra et al., 1957).

The presented literature studies of Misra *et* al. (1957, 1956) have been evaluated as literature source to cover the requirements set up in the current guidance for efficacy of biocidal products for product type 18 [Guidance on the BPR: Volume II Parts B+C Version 3.0 April 2018]. According to the requirements set for literature data and respective reports the following conditions to proof scientific robustness have to be met in chapter 3.1.2 [3]:

i) Scientific robustness of the study
   a. Number of replicates
   b. Conditions of the test (temperature, humidity,…)
   c. Data on the test substance
   d. Tested organisms
   e. Description of method
   f. Applicability of application method
   g. Raw data

The presented literature studies may be regarded as tier 1 screening tests. The tests have been performed using *Musca nebulo* which is regarded as part of the group of house flies which is associated with anthropogenic habitats. In Europe, the main representative organism is *Musca domestica* which thus is required as surrogate organism for a claim against house flies. To allow a read across between *Musca domestica* and *Musca nebulo* a justification should be provided which demonstrates the comparable susceptibility of both common insecticides. The literature studies have been performed in duplicates. According to the requirements set up by the guidance for efficacy (Guidance on the BPR: Volume II Parts B+C Version 3.0 April 2018) quadruplicates are recommended in the specific description of tier 1 tests for flies and in the general requirements at least triplicates are required. Following the description of the test method the size of the test cage is not specified. Furthermore, no raw data is available for the performed studies. In conclusion, the presented studies may be regarded as Klimisch 2 studies. Which are in its own right scientifically robust but do not totally comply with specific guideline requirements in force today. The studies may not be regarded as key studies but are suited to be used as supplementary studies.

Several other studies evaluate the effects of a range of compounds related to DDT, including BCPS, on a variety of arthropod species (Läuger *et* al. 1944, Proverbs and Morrison 1946, Deonier *et* al 1946, Metcalf 1948, Browning *et* al. 1948). The reports are different as regards their scope and the level of detail included. The mentioned publications include reviews summarizing the results of testing conducted by commercial companies (Läuger et al. 1944, Läuger 1944) or tests reported in previous publications (Deonier et al 1946), as well as reports describing the experimental testing of different compounds (Proverbs and Morrison 1946, Metcalf 1948, Browning et al. 1948). All work is addressing the insecticidal or acaricidal properties of the respective compounds in relation to the activity of DDT and DDT analogues, however the reports address different routes of exposure (contact with treated surfaces, spray application, consumption of treated materials) and effects on different species, including

1) *Drosophila melanogaster* exposed to coated glass vials (Proverbs and Morrison 1946, Browning et al. 1948) and impregnated filter paper (Proverbs and Morrison 1946) or exposed by aerosol sprays (Proverbs and Morrison 1946)

2) *Anopheles quadrimaculatus* (4th instar mosquito larvae) exposed to an acetone/water suspension containing the test substances (Deonier et al 1946)

3) Greenhouse thrips (*Heliothrisps haemorroidalis*) and citrus red mites (*Paratetranychus citri*) exposed to coated surfaces of citrus fruits (Metcalf et al. 1948)

4) Cloth moth (Tineola biseliella) exposed to fabric treated with test substances (Läuger et al. 1944, Läuger 1944)

The results of Proverbs and Morrison, 1946 and Browning et al. 1948 indicate that BCPS is not effective as a contact agent to kill *Drosophila melanogaster*. BCPS was used by Proverbs and Morrison 1946 at a concentration of 50 mg/10 ml acetone to coat glass test vials. For testing 10 of the coated vials were loaded with 15 flies each (adult flies 4-6 days after emergence of a uniform age) and the mortality rate was scored after 18 or 24 hours of exposure. Control exposures were done with acetone alone, which consistently resulted in mortality rates of less than 2 % (see Proverbs and Morrison 1946 and Browning et al. 1948). As a measure of potency the insecticidal activity of different doses of purified DDT dissolved in acetone was measured (test concentrations: 0,25 mg /10 ml, 0,5 mg /10 ml, 0,75 mg/10 ml, 1,0 mg/10 ml, 1,5 mg/10ml, 3,0 mg/10 ml and 10 mg/10 ml). 50 % mortality was recorded after exposure of flies for 18 hrs to vials coated with 1 mg DDT/10 ml acetone solutions and after exposure for 24 hrs to vials coated with 0,5% mg DDT/10 ml acetone. Exposure to filter paper impregnated with DDT (at similar concentrations as with the coated vial technique) and exposure to DDT sprays resulted in comparable mortalities (Proverbs and Morrison 1946), however the effective DDT dose for the exposure to impregnated filter paper was slightly higher than the one for the coated vial technique reflecting minor differences in exposure to and availability of the agent (1,0 mg DDT/10 ml acetone needed to achieve a 50% mortality after 24 hrs). BCPS tested at a concentration of 50 mg BCPS/10 ml acetone was recorded to be not effective in the coated vial test.

Browning et al. (1948) used a comparable testing approach (coated vial method; 500 – 1500 individual flies tested in total in 5-100 replicates depending on test sizes, 1 mg DDT/100 ml acetone used as a positive control). BCPS was determined to have "nil" insecticidal activity for Drosophila, which according to Browning *et* al. 1948 is a measure of 500 mg test substance/100 ml acetone resulting on no increased mortality after 18 hrs at 25° Celsius. According to Browning et al. (1948) BCPS is 10 times less soluble in olive oil than DDT, however shows a higher degree of mammalian toxicity (60 times higher than DDT, but not resulting in symptoms correlated with neurotoxicity).

The insecticidal potency of compounds related to DDT towards mosquito larvae is evaluated in Deonier et al (1946). Test compounds as well as pure DDT as a standard were solubilized in acetone and 20 early 4th instar larvae of *Anopheles quadrimaculatus* were exposed to DDT or the test substances in deionized water at concentrations of 10 ppm for 24 and 48 hours. Compounds that resulted in more than 50% mortality at the initial dose after 48 hrs were further tested using successively lower test concentrations (1,0 ppm, 0,1 ppm, 0,05 ppm, 0,025 ppm, 0,01 ppm, 0,005 ppm, 0,0025 ppm). Pure DDT resulted in mortalities of approx. 80% at the lowest concentration (0,0025 ppm). Deonier et al (1946) indicate that compounds which are closely related to DDT generally result in a higher toxicity for mosquito larvae. p,p´-dichlorodiphenyl sulphide, a compound related to BCPS is listed having lower toxicity to mosquito larvae. BCPS is not referred to in the available text, however the 3rd page of the publication (p 139 containing Table 2) is missing from the copy submitted by the registrants and is not available publicly. Table 2 is listing the lowest concentrations at which the tested compounds were toxic to the tested larvae and is thus relevant to assessing whether BCPS was tested in the study. In case BCPS was included

the missing Table 2 should indicate the relative level of toxicity compared with either DDT and p,p´-dichlorodiphenyl sulphide.

Metcalf (1948) reports on the acaricidal properties of DDT and other related compounds, including BCPS and p,p´-dichlorodiphenyl sulphide, on two arthropods citrus pests, greenhouse thrips (*Heliothrisps haemorroidalis*) and citrus red mites (*Paratetranychus citri*). For testing oranges were coated with test substances by dipping them for 1 sec into (1% w/v) solutions of the respective test substance in acetone. After drying 25 adults of thrips or mites were exposed to a treated orange. Assays were replicated 3 times with 100 individuals of thrips or mites tested in total. Mortalities were recorded after 24 and 48 hrs respectively. In case a substantial mortality was recorded during an assay, the test was repeated with half the previous dose (with one replication). DDT is toxic to *Heliothrisps haemorroidalis* (50% mortality at 0,001% after 24 hrs exposure), however nontoxic to *Paratetranychus citri* (at 10% after 24 hrs exposure). The objective of the study was to identify substances with a higher toxicity towards *Paratetranychus citri* and possibly other tetranychid mites, which could not be controlled by DDT or other chlorinated hydrocarbon insecticides. Metcalf (1948) reports a definitive acaricidal activity among others for 1,0% p,p´-dichlorodiphenyl sulphide (96% mortality after 48 hrs), however no such activity for BCPS at 1,0%. Both substances were not toxic to thrips at a concentration of 1,0%.

Läuger *et* al. (1944) review the toxic activity of natural and synthetic substances, including DDT as well as BCPS and p,p´-dichlorodiphenyl sulphide, towards different insects and in particular to larvae of cloth moths (*Tineola biselliella*) upon consumption. The objective of the paper is to describe compounds which are highly effective against such pests after ingestion, yet may be impregnated tightly onto fabrics made of wool (an aspect described in more detail in Läuger 1944). The paper lists a multitude of compounds assessed for such characteristics, however offers little detail on the methods used to test the biological activity of the assayed substances. It also does not give quantitative results of the testing but uses a scoring system which is based upon the following grouping: The activity of the compounds is scored either as "not effective", "slightly effective" (or "bad"), "effective" (good), "highly effective" ("very good"). The scoring terms are not used in a strict manner, which results in some ambiguity as regards the specific qualifications. The paper however distinguishes the category of "highly effective" ingestible toxicants, such as BCPS, from substances like DDT which act as contact toxicants and are classified as being of "highest toxicity" to fabric pests upon contact or ingestion.

While BCPS and related compounds are not compared with DDT and other contact insecticides directly due to their different exposure pathway, they are described by Läuger *et* al. (1944) as "highly effective" toxicants after ingestion.
To further assess this conclusion more information was included in the publication by Läuger *et* al. (1944) concerning the testing methods used to conduct the bioassays to meet the criteria contained in the Guidance on the BPR: Volume II Parts B+C (Version 3.0 April 2018) mentioned above. Furthermore, data on the results of the testing are needed for an appropriate assessment. The information presented by Läuger *et* al. (1944) however suggests that such an assessment should be conducted.
In addition, the information compiled by Läuger *et* al. (1944) indicates that BCPS may be toxic to other insects than *Tineola biselliella* which act upon ingestion of the substance, even if it is not acting as a contact toxicant in these species.

Summary

Based on the general information given by Läuger *et* al., 1944, BCPS is an excellent stomach insecticide "*Aus früheren Arbeiten in einem andern Gebiet besassen wir noch das p, p'-Dichlordiphenylsulfon. Als Frassgift zeigte die Substanz eine für uns bis dahin nie*

gesehene überragende Wirksamkeit." Results from Läuger need to be treated with caution, as the author was accused of fraud concerning scientific results [17].

Insecticidal activity of BCPS is better than that of DDT, at least against fly *Musca nebulo* (Misra et al., 1957).

Results have been obtained only with caterpillars of clothes moths, which had a restricted food consumption (keratin). Interestingly, only the p´, p halogenated form had the highest activity. BCPS is assumed as not lipophilic enough for contact insecticidal activity.

In contrast, DDT is, based on the additional C(Cl3)-group, more lipophilic, and can thus penetrate cell membranes.

BCPS and DDT are very close related substances, the mode of action is assumed to be similar. For the activity of DDT and BCPS, it is a pre-requirement that the –Cl substituents on the benzolic ring are para substituted. BCPS is a stomach insecticide, whereas DDT is a contact insecticide due to the additional lipophilic C(Cl3)-group.

7.8.3. Microbiological activity in sewage treatment systems

In a limit test according to OECD TG 209 using activated sludge from a Swiss waste water treatment plant treating predominantly domestic waste water (Unpublished study report, 2009a) as well as in OECD TG 209 test using activated sludge from a German municipal wastewater treatment plant (Unpublished study report, 2009b) no effect was observed at 1000 mg/L, which is far above the water solubility of 0.86 mg/L. In conclusion water solute BCPS was not toxic to micro-organisms.

7.8.4. PNEC derivation and other hazard cconclusions

Not evaluated.

7.8.5. Conclusions for classification and labelling

Based on the observed NOEC values from both the long-term daphnid reproduction study (0.32 mg/L) and algal growth inhibition study (0.28 mg/L) on BCPS, and the non-rapid biodegradability of the substance, the environmental hazard classification should be Aquatic Chronic 2 in accordance with EC Regulation 1272/2008. After discussions with the Registrant(s) in the course of this substance evaluation the classification was updated from Aquatic Chronic 4 to Aquatic Chronic 2 by the Registrant(s). No harmonised classification is proposed at the moment.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The toxicokinetic behaviour of BCPS was studied in rats after single intravenous and oral application and after repeated oral administration of radiolabelled BCPS. In the repeated dose toxicity study (gavage, 7 days) also hepatic enzyme induction has been determined (Mathews et al., 1996).

In a further repeated dose study (Poon et al., 1999) the distribution of unlabelled BCPS, as well as hepatic enzyme induction and the toxicological effects of BCPS (see also 7.9.4 repeated dose toxicity) were investigated in rats.

[17] https://www.research-collection.ethz.ch/bitstream/handle/20.500.11850/148165/eth-30391-01.pdf

There are no experimental data available on BCPS toxikokinetics following dermal or inhalation exposure.

Table 19: Overview of experimental studies on absorption, metabolism, distribution and elimination

Method	Results	Reference/Remarks
Toxicokinetic study Test species: rat (Fischer 344) male Number of animals: 4/group Test material: unlabelled BCPS (Purity: 98%), 14C-BCPS (Purity: 96%) Vehicle: Emulphor EL-620 Number of animals: 4/group <u>Single dose experiments:</u> Study A: Intravenous application (i.v.), 10 mg/kg bw, observation period 21 days post treatment Study B: Oral gavage, 0, 10, 100, 1000 mg/kg bw, 3d (72 hr) post treatment observation <u>Repeated dose experiments:</u> Study C: 7-day repeat dosing experiment, observation 3 d (72 h) after repeat dosing; oral gavage, 1, 10, 100 mg/kg bw/d Study D: 2, 3 and 5 weeks repeat dosing with 5 d/wk; oral gavage, 10 mg/kg bw/d	Absorption: high oral absorption (appr. 80% to 90%) Distribution: rapid distribution out of blood into tissues; high levels in adipose tissue; distribution pattern: adipose tissue >> skin > muscle > liver > blood > kidney Increasing accumulation of BCPS in adipose tissue was observed up to 24 hrs, followed by slow elimination with a half-life in adipose tissue of 12 days in adipose tissue Metabolism: The radiochemical content in adipose tissue peaked after 3 weeks (15.3% of the dose), and adipose concentration declined to 6.7% by week 5. In the 3 and 5 week repeat dosing study the amount excreted during the final week was around 100% of the total dose administered. This indicates that the steady state has been reached after around 2-3 weeks. CYP450 and EROD (CYP 1A1/2) were increased in the 1 and 10 mg BCPS /kg bw/d group and in the 100 mg/kg bw/d group modest CYP450 increase no EROD increase	Mathews JM, Black SL and Matthews HB (1996) Klimisch 2 similar to OECD Guideline 417 (Toxicokinetics)
Test species: rat (Sprague-Dawley), male Number of animals: 6 animals/group, 10 groups Test material: BCPS Purity: >99% Vehicle: corn oil Exposure duration: 28 days	Distribution: percentage of total dose in adipose >> liver > kidneys >lung >spleen > brain remaining constant; in kidneys levels increased until end of study; retained substance in tissue increased with dose Increase of BROD (benzoylresorufin O-	Poon R. et al., (1999) Klimisch 2 Experimental study, non GLP, not guideline conform, presentation of methods and data sufficient

Method	Results	Reference/Remarks
Application route: oral feed study Dose levels: 10, 100, or 1000 ppm in diet corresponding to 0.8±0.1, 8.1±1.3, and 75.6±8.4 mg/kg bw/d time course setting, administration of 75.6 mg/kg/d BCPS diet, animals were sacrificed at the end of week 1, 2, 3 and 4 and adipose tissue, liver, and kidneys were analysed for BCPS residues	dealkylase) and PROD (pentoxyresorufin O-dealkylase) (CYP2B enzymes) and induction of GST (Glutathione S-transferase) and UDPGT (UDP-Glucuronosyltransferase) in a dose dependent manner, EROD (Ethoxyresorufin-O-deethylase) no effect, MROD (Methoxyresorufin O-demethylase) (CYP1A enzymes) even decreased (see text). Most pronounced toxic effect: liver (hepatomegaly), urinary ascorbic acid increase (metabolite of the glucuronic acid pathway), hypercholesterolemia, increased hepatic TBARS (thiobarbituric acid reactive substances)	

The toxicokinetic studies indicate that BCPS is nearly completely absorbed and rapidly distributed to tissues, especially to adipose tissue (concentration in adipose tissue >> skin > liver > blood >kidney > brain, spleen, lung).

Increasing dose in adipose tissue of BCPS was observed up to 24 hrs, followed by a low elimination rate, a terminal half-life of 12 days was determined in adipose tissue (single i.v. application, 10 mg/kg bw). The BCPS equivalents in tissues were primarily parent unmetabolised compound. An increase in metabolism has been observed in relation to dose and time (Mathews et al., 1999), e.g. a peak in tissue concentration was observed by week 2-3 in the repeated dose study (10 mg/kg bw over a time-period of 5 weeks, vehicle: Emulphor), followed by a decrease in tissue concentration after 5 weeks. The altered mechanism can be explained by the fact that BCPS induces metabolic hepatic enzymes. Data indicate that the vehicle Emulphor itself induces CYP450 and thus it is not clear if and to which extent the vehicle has an influence on the observed altered metabolism (NTP, 2001).

In the study of Poon et al. (1999) in which BCPS (75.6±8.4 mg/kg bw/d, diet, vehicle: corn oil) was applied to Sprague Dawley rats no decrease of BCPS content was found in tissues between week 1 and 4, even an increase in kidneys were observed at week 4.

Studies demonstrate that BCPS has the capability to induce hepatic enzymes such as CYP450 enzymes, UDPGT and GST. Liver enzyme induction is also dose dependent, e.g. in the study of Mathews it is demonstrated that parameters associated with CYP1A activity were at the 10 mg/kg bw/day group applied for 7 days twice that from rats administered only vehicle or 1 mg/kg bw/day BCPS. Comparing the available information a clear pattern of enzyme induction (e.g. which kind of CYP450 are induced) cannot be deduced (Poon, 1999, Mathews, 1996). Differences between enzyme induction pattern in the aforementioned studies might be explained by various factors, e.g. different rat strains, exposure duration, vehicle and/or BCPS application.

The excretion of BCPS is rather slow and predominantly via faeces. The excretion of BCPS is dependent on metabolism to more polar compounds (mono-hydroxy-BCPS and its glucuronide), and relatively little parent compound was excreted before metabolism.

The registrants provided further information based on QSARs for predicting total elimination half-lives (HLT) and biotransformation half-lives (HLB) in humans (Joint registration consortium (2020). These predictions indicate a biotransformation half-life (HLB) of 2.5 to 6.9 days and a total elimination half-life of 0.8-4.4 days.

Registrants also calculate preliminary BMF values from the rat studies (Mathews et al., 1996, Poon et al., 1999), which indicate low BMF values (Joint registration consortium (2020)). These calculations, however, also prone some uncertainties since for example lipid content of the diet is not known and there is no guidance how to normalize data to generate meaningful BMF values from rat data.

7.9.1.1. Conclusion on toxicokinetics

The eMSCA concludes that animal data indicate a rapid distribution of un-metabolised BCPS mainly into adipose tissue, where a half-life of 12 days was observed after single application. The elimination half-life of 12 days might be due to BCPS's high affinity to adipose tissues. Accelerated clearance was observed after repeated dosing explained by liver enzyme induction by BCPS in the experiments of Mathews et al. (1996). The steady state after repeated dosing is reached after 2-3 weeks indicating a lower half-life (~5 days) after repeated dose application. A decrease in content of BCPS in tissue after repeated dosing was not substantiated in a further repeat dose study, in which the content of BCPS remained unchanged between week 1 and 4 (Poon et al., 1999), but did not increase. No information concerning low dose application is available, which would be of interest since liver enzyme induction is dependent also on applied dose.

The level to which BCPS might have the property to accumulate is dependent on factors like BCPS exposure pattern (e.g., concentration) and moreover on induction of liver enzymes in individuals or wildlife species, which have the capacity to metabolise BCPS. Hereby, it is noteworthy, that the capacity to eliminate BCPS might underlie a huge variation between species.

For example, it is known that for structural analogues of BCPS such as polychlorinated biphenyls the half-life in rat is relatively short (approx. range from 10-400 days) compared to humans (several years) due to in part higher rate of metabolism. Data indicate that there is evidence that BCPS can be detected in human biomonitoring samples (e.g. human liver samples). However, no further information on accumulation potential in humans is available.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity

Acute toxicity: oral

Two acute oral toxicity studies demonstrate that no classification for the oral route is required. The obtained LD50 values are above 2000 mg/kg bw (Unpublished study report, 1981, Unpublished study report, 2000). The eMSCA supports the registrant(s) conclusion that BCPS is not acute toxic via the oral route.

Acute toxicity: inhalation

Testing for the inhalative route is only appropriate if exposure of humans via inhalation is likely, taking into account the vapour pressure and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size (REACH, 8.5.2, Column 2). Waiving for acute inhalation toxicity should be considered for low volatility substances, which are

defined as having vapour pressures <1 x 10^{-5} kPa for indoor uses, and <1 x 10^{-4} kPa for outdoor uses (ECHA, 2017). Based on the estimated vapour pressure of BCPS of 1.5 x 10^{-8} kPa at 25°C and the particle size distribution (PM100: <8%, PM10: 0%) the eMSCA considers that inhalation exposure is not of concern and thus the waiving of acute inhalative toxicity is justified.

Acute toxicity: dermal

No reliable study is available for the acute dermal toxicity endpoint. Phys-chem data and modelled data indicate that the dermal absorption is moderate. This assumption together with data on no acute oral toxicity of BCPS indicates that acute dermal toxicity is not of concern.

Acute toxicity: other routes

Information on acute toxicity in a further species is provided using the intraperitoneal route (Unpublished study report, 1991). Mice have been exposed to BCPS and a LD50 of 2448 mg/kg bw was derived. The results substantiate the low acute toxicity potential observed in oral rat studies.

Acute toxicity: conclusion

The eMSCA concludes that the substance is not acute toxic based on the available information.

Irritation/Corrosion

Skin irritation/corrosion

No skin irritation study is available, which is performed according to current test guidelines. The key skin irritation study has significant deviations from the OECD TG 404 (Acute dermal irritation/corrosion) (Unpublished study report, 1981). Three rabbits were exposed to BCPS (500 mg/application site) for 24 hrs (instead of 4 hrs as recommended in the guideline) using an occlusive dressing (instead of a semi-occlusive). The test item was applied on intact as well as on scarified skin (not recommended in the TG). The animals were observed 24 and 72 hrs and 8 days post application (time points in the TG 24, 48 and 72 hrs, and 14 days post application). Draize scoring system was used. For the intact skin very slight erythema (mean score 0.8) and no oedema were observed at 24 and 72 hrs post application. Desquamation only to a very mild degree (in 2 out of 3 animals) was observed 8 days post application. Therefore no classification is proposed.

This observation was further supported by two skin irritation studies, which however, are insufficiently reported (Unpublished study report (1970), (1976b) and thus not reliable or even not assignable. In the LLNA (local lymphnode assay) no skin irritation reaction has been observed on the application sites of mice ears (Unpublished study report, 2010b).

The eMSCA concludes that a classification for skin irritation is not warranted based on the available data.

Eye irritation/corrosion

No eye irritation study is available, which is performed according to current test guidelines. The key eye irritation study has significant deviations form OECD TG 405 (Acute Eye Irritation/Corrosion) (Unpublished study report, 1981). In this study 78 mg of grained BCPS was instilled in the conjunctival sac of each eye of three rabbits. In contrast to the recommendation of the guidance no washing was performed after 24 hrs. The animals were observed 1, 24, 48 and 72 hrs and on day 8 post application (time points in the TG 405 at least 1, 24, 48 and 72 hrs, 7 days, 14 days and 21 days post application). The Draize scoring system was used.

The mean cornea score and mean iris score were 1 and the mean conjunctivae score and mean chemosis score were 2 in all tested animals at time-points 24 hrs, 48 hrs, 72 hrs after application. At the end of the observation period (day 8 after application), chemosis and iris effects had resolved.

Cornea (score 1 in 1/3 animals) and conjunctivae effects (score 1 in 3/3 animals) were not fully reversible. Also scar formation was noted in all test animals at the 48 hrs and subsequent readings. It is acknowledged, that based on the effects observed a clear discrimination between primary irritating and/or secondary irritation based on mechanical distress caused by the solid, nearly insoluble test substance in the unwashed eyes is not possible. Furthermore, due to the very short observation period (8 days vs OECD TG 405 21 days) the reversibility cannot be addressed.

The observation of mild eye irritation is supported by a further eye irritation study (Unpublished study report, 1976a). In this study 44 mg (solid) BCPS was applied to the right conjunctival sac of two albino rats. After 20 seconds of treatment one of the two eyes was washed with tap water. The observation period was up to seven days post-application. The effects on conjunctivae, iris and cornea were mild to very mild and no effects were reported at day seven, indicating that effects of BCPS application are reversible. The investigation, however, is not sufficiently reported (Klimisch Score 3: not reliable). In a further report no eye irritation potential of BCPS was observed (Unpublished study report, 1970), however due to lack of experimental details the study is not assignable (Klimisch 4).

The scar formation at the end of the observation period in the key study might be evidence that the effect is irreversible; nevertheless due to short post-application period no unambiguous conclusion can be drawn on reversibility of the effect.

The eMSCA supports the conclusion of the registrants that BCPS fullfills the classification criteria laid down in Regulation 1272/2008/EC (CLP Regulation) for Eye Irrit. Cat. 2. No harmonised classification is proposed at the moment.

7.9.3. Sensitisation

The key study is a GLP compliant local lymphnode assay (LLNA) carried out according to OECD TG 429 (Unpublished study report, 2010b). BCPS was applied to the ears of 4 female mice at concentrations of 0, 5, 10 or 25% (w/v). No signs of local irritation were noted during the study. Low and mid dose group animals (5 and 10 % BCPS) showed no signs of systemic toxicity. One animal died in the high dose group (25 % BCPS). The remaining animals at the highest dose showed no symptoms of systemic toxicity. The stimulation indices were 1.62, 0.83 and 1.00 at 5, 10 and 25 % BCPS, respectively. No EC3 value was established. The positive control (Hexyl cinnamic aldehyde) induced the appropriate response over background (EC3 value: 12.9 %). The study does not demonstrate skin sensitisation properties of BCPS.

The finding is supported by a further non-guideline conform dermal sensitisation study (Unpublished study report, 1970). In this study application 10 % solution of BCPS was applied to the ears of three albino guinea pigs for 3 days. The application did not result in skin sensitisation. Due to poor reporting this study is, however, not assignable (Klimisch Score 4).

The eMSCA supports the conclusion of the registrants that BCPS has no skin sensitising potential.

7.9.4. Repeated dose toxicity

For the evaluation of the endpoint repeated dose toxicity results from five animal experiments - two subchronic (14 weeks) studies with rat and mice, two chronic (2 years)

combined repeated dose/carcinogenicity studies with rat and mice (NTP, 2001) and sub-acute toxicity test with rat (Poon et al., 1999) are considered.

Study details, main results and remarks are depicted in table 20.

Table 20 Study on repeated dose toxicity

Study/Method	Results	Remarks/ Reference
Test species: rat (Fischer 344) male/female Number of animals: 10/sex/dose Test material: BCPS Vehicle: no vehicle Study duration: subchronic – 14 weeks Dose levels: 0, 2, 6, 19, 65 and 200 mg/kg bw/d (corresponding tg to 0, 30, 100, 300, 1000 or 3000 ppm) Application route: Feed mixed with the test substance was available ad libitum equivalent or similar to OECD TG 408 (repeated dose 90 day oral toxicity in rodents)	Dose dependent liver weight increase (up to +135%), dose dependent increase in centrilobular hepatocyte hypertrophy, cytomegaly and karyomegaly Increased incidences in nephropathy Organ weight changes: absolute and relative thymus decrease (m), absolute thymus decrease (f), absolute and relative kidney increase (m), relative kidney increase (f), absolute and relative testis increase NOEL: 2 mg/kg bw (based on liver weight ↑ associated by hypertrophy of centrilobular hepatocytes (at 6 mg/kg bw/d); no NOAEL	NTP (2001) Klimisch 2 Key study GLP - addition of neurobehavioural examination - test conducted prior to OECD TG update to include endocrine disruptor relevant endpoints - urine analysis lacking
Test species: mouse (B6C3F1) male/female Number of animals: 10/sex/dose Test material: BCPS Vehicle: no vehicle Study duration: subchronic – 14 weeks Dose levels: 0, 3.5, 15, 50 165, 480 mg/kg bw/d (corresponding to 0, 30, 100, 300, 1000 or 3000 ppm) Application route: Feed mixed with the test substance was available ad libitum equivalent or similar to OECD TG 408 (repeated dose 90 day oral toxicity in rodents)	Dose dependent liver weight increase (up to +107.3%), dose dependent increase in centrilobular hepatocyte hypertrophy and significant induced incidences of focal hepatocyte necrosis in males in the highest dose groups (165 and 480 mg/kg bw/d) Organ weight changes: relative testis increase, relative kidney weight increase (m, f), relative ovaries and uterus increase, absolute thymus increase (f) NOEL: 3.5 mg/kg bw (based on liver weight increase associated by centrilobular hepatocyte hypertrophy noted at 15 mg/kg bw/d); NOAEL: 50 mg/kg bw/d (focal hepatocyte necrosis at 165 mg/kg bw/d)	NTP (2001) Klimisch 2 Key study GLP - addition of neurobehavioual examination - test conducted prior to OECD TG update to include endocrine disruptor relevant endpoints - no clinical chemistry,urine analysis lacking

Study/Method	Results	Remarks/ Reference
Test species: rat (Fischer 344) male/female Number of animals: 50/sex/dose Test material: BCPS Vehicle: no vehicle Dose levels: 0, 0.5, 1.5, or 5.0 mg/kg bw/day corresponding to 0, 10, 30, or 100 ppm (males) 0, 1.6, 5.4, or 17 mg/kg bw/d corresponding to 0, 30, 100, or 300 ppm (females) Study duration: 105 to 106 weeks Application route: Feed mixed with the test substance was available ad libitum equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity/ Carcinogenicity Studies)	Centrilobular hepatocyte hypertrophy (males and females), significant bile duct hyperplasia and centrilobular degeneration (females) NOAEL: 1.5 mg/kg bw/d (bile duct hyperplasia centrilobular degeneration noted in females at 5.4 mg/kg bw/d, for males/females hepatocyte hypertrophy at 5/5.4 mg/kg bw/d)	NTP (2001) Klimisch 2 Supporting study GLP - no haematological examination, no urin-analysis, no clinical chemistry - determination of BCPS in plasma
Test species: mouse (B6C3F1) male/female Number of animals: 50/sex/dose Test material: BCPS Vehicle: no vehicle Dose levels: 0, 4, 13 or 40 mg/kg bw/day corresponding to 0, 30, 100 or 300 ppm (males) 0, 3, 10 or 33 mg/kg bw/day corresponding to 0, 30, 100 or 300 ppm (females) Study duration: 105 weeks to 106 weeks Application route: Feed mixed with the test substance was available ad libitum	Centrilobular hypertroyphy, eosinophilic foci (only females) NOEL: 3 mg/kg bw/d (based on centrilobular hepatocyte hypertrophy noted in female rats at 13 mg/kg bw/d); no NOEL for males identified (≤ 4 mg/kg bw/d) NOAEL: 10 mg/kg bw/day (based on eosinophilic foci (female))	NTP (2001) Klimisch 2 Supporting study GLP - no haematological examination, no urinanalysis, no clinical chemistry - determination of BCPS in plasma

Study/Method	Results	Remarks/ Reference
equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity/ Carcinogenicity Studies)		
Test species: rat (Sprague-Dawley), male Number of animals: 6 males/group, 10 groups Test substance: BCPS Dose levels: 0, 10, 100, or 1000 ppm in diet corresponding to 0, 0.8, 8.1, and 75.6 mg/kg bw/d Study duration: 28 days Application route: oral feed study Time course setting: administration of 75.6 mg/kg bw/d BCPS, animals were sacrificed at the end of week 1, 2 and 3, adipose tissue, liver, and kidneys were analysed for BCPS residues	distribution: percentage of total dose in adipose >> liver > kidneys >> lung >spleen > brain remaining constant; in kidneys levels increased until end of study; retained substance in tissue increased with dose Induction of BROD and PROD (CYP2B related enzymes) and induction of GST and UDPGT, MROD (CYP1A2 related enzyme) even decreased Most pronounced toxic effect: liver (hepatomegaly), urinary ascorbic acid increase (metabolite of the glucuronic acid pathway), hypercholesterolemia, increased hepatic Thiobarbituric acid reactive substances (TBARS) NOAEL: 8.1 mg/kg bw/d (based on liver weight increase, increased blood cholesterol concentration)	Poon R. et al., (1999) Klimisch 2 - not guideline conform

Liver effects

The liver is the target organ of BCPS exposure in rats and mice. Negative impact on liver was observed in all repeated dose toxicity studies. The effects are mainly characterised by marked liver weight increase and centrilobular hypertrophy. The severity of this lesion increased in a dose dependent manner and was characterised mostly minimal to mild.

Beside liver weight increase and centrilobular hypertrophies following liver toxicity related findings were observed in the repeated dose toxicity studies:

In the 14 week mouse study also significantly increased incidences of focal hepatocyte necrosis were detected in males in the higher dose groups (165 and 480 mg/kg bw/day). In the 14 week rat study changes in sorbitol dehydrogenase activity and bile acid concentrations were consistent with the liver lesions observed histopathologically in rats. Alkaline phosphatase activity decreased in an exposure-related manner. Alanine aminotransferase activity, another marker of hepatocellular health, was not affected similarly and, in fact, demonstrated decreased activity in the lower dose groups. In the chronic (2 years) mouse toxicity study centrilobular degeneration of the liver has been significantly increased only in females at 5.4 mg/kg bw/d (10 out of 50) and 17 mg/kg bw/d group (7/50). It is noteworthy, that the incidence of centrilobular degeneration and severity in male rats was generally high (control group: 18 out of 50) irrespective of BCPS administration. In the chronic (2 years) rat toxicity study significant increased incidence of eosinophilic foci were observed only in females in the high dose group (33 mg/kg bw/d).

In the 28 day toxicity study of Poon et al. (1999) it is demonstrated that BCPS induces hepatic enzyme activities already at very low doses (0.8 mg/kg bw/d). A clear increase in BROD and PROD, which are CYP2B related microsomal enzymes was observed already at a dose level of 0.8 mg/kg bw/d. Whereas EROD activity, enzyme associated with the CYP1A1 level has not changed and MROD activities (related to CYP1A2) even decreased. In this study significant increase of the phase II enzymes UDPGT and GST has been observed at a dose level of 8.1 mg/kg bw/d and above. Urine analysis reveals an increase in ascorbic acid (up to 16.7 fold) already significant at the lowest dose group (0.8 mg/kg bw/d).

A threefold increase in serum cholesterol levels has been observed at the highest dose (75.8 mg/kg bw/d), which demonstrates a serious perturbation in homeostasis of lipids and lipoproteins. The increase is considered as adverse since hypercholesterinemia has an impact on the development of coronary arterial diseases. Also the increase in hepatic Thiobarbituric acid reactive substances (TBARS) indicates dysfunction in lipidmetabolism. According to the study authors, the significance of the dose related decrease in serum LDH is not clear. Adverse effects such as liver disease, myocardial infarcts and hemolyisis is rather associated with increase and not decrease of the enzyme. In the study of Poon et al. (1999) BCPS application has no significant influence on N-acetylglucosaminidase (NAG), protein and haemoglobin levels in the urine. Hepatic liver enzyme induction was also observed in the study of Mathews et al. (1996). However, comparison of the results does not allow identifying a clear pattern of enzyme induction (e.g. which types of CYP450 are induced).

Other relevant observations:

In the 14 week rat study (NTP, 2001) the thymus weight reductions were statistically significant in both absolute and relative thymus weight, with the top dose being relatively severe and adverse (66% of control absolute weight, 82% of control as relative weight). In the female rats, there were statistically significant reductions in absolute thymus weight (77% of control at top dose), but the values for relative weight (93% of control at top dose) were not significantly different. These effects have been considered in the study design of the planned EOGRTS.

In the 14 week study in rat the only neurotoxicological finding observed was a statistically significant decrease in landing hindlimb footsplay of male rats in the 65 mg/kg bw/day dose group (-14.8%, $p \leq 0.01$), a similar effect was not evident in female rats. No data for 200 mg/kg bw/day (top dose) are presented in this study. In the 14 week study in mice the only neurotoxicological finding observed was a statistically significant decrease in hindlimb grip strength in males at 6 mg/kg bw/day. However, no significant changes were observed at 19 mg/kg bw/day and 65 mg/kg bw/day. The top dose was not examined. Moreover, it is noted that there is a concern for neurotoxicity based on neurotoxic effects of structural analogues like polychlorinated biphenyls.

In the 14 week rat study also the incidence of nephropathy was increased in females at dose levels of 65 or 200 mg/kg bw. Dose-related increase in severity of nephropathy was also observed in male rats. The male rats had also statistically significant relative and absolute right kidney weight increase at the highest two groups, whereas the female rats had only relative right kidney weight increase at the highest two dose groups.

In the oral 14 week rat study a statistically significant increase was observed at 19 mg/kg bw/d for relative testis weight (7.9%, $p \leq 0.01$) and for the relative and absolute testis weight at 65 mg/kg bw/day (17.1% for relative weight, $p \leq 0.01$, and 5.3% for absolute weight, $p \leq 0.05$) and 200 mg/kg bw/d (30% for relative weight, $p \leq 0.01$, and 3.4% for absolute weight, $p \leq 0.05$). In female rats ovaries and uterus weight were not changed. In the 14 week toxicity study in mice also a significant increase of relative right testis weight was observed in the two highest dose groups (165 mg/kg bw/d: 9.2%, 480 mg/kg bw/d: 17.6 %, both $p<0.01$). Relative weight of ovaries was significantly increased from 50 mg/kg bw/d onwards (16.9% at 50 mg/kg bw/day, $p<0.05$). The relative weight of uterus

was increased in the two highest dose groups (47.1% at 165 mg/kg bw/d and 40.4% at 480 mg/kg bw/d, both p<0.01).

Conclusion

The eMSCA concludes that the main target organ of BCPS toxicity is the liver. Liver weight increase in absence of pathological changes (such as degenerative lesions, cell proliferation and necrosis) is considered to be an adaptation. Increased liver weight and centrilobular hypertrophy might be considered as adaptive response (CLP Annex I, 3.9.2.8.1 (d)).

Present data indicate also some histopathological evidence of structural degeneration and necrotic changes. Based on the present data set it cannot be unambiguously excluded that other mechanisms might lead to adverse effects e.g. oxidative stress. For example it is mentioned in the NTP report (NTP, 2001) that adverse effects may possibly arise from increased mixed-function oxidase activities that cause altered sensitivities toward hepatotoxins or carcinogens.

However, comparing the effect levels with the limit for classification it can be summarised that adverse effects (e.g. liver necrosis) occur mostly above the limit for classification and if effects were observed below the limit of classification (e.g. centrilobular degeneration in 2-year rat study, females) the severity was only minimal to mild and therefore not considered adverse. Based on the comparison of nature and strength of the observed effects with the classification criteria of the CLP Regulation no classification for STOT RE is proposed.

Furthermore, organ weight changes of the thymus and of testis have been observed and there is some concern for neurotoxicity (see above). An EOGRTS with the cohorts 1A and 1B (Reproductive toxicity) and cohort 3 (Developmental immunotoxicity: due to observed effects on thymus) is pending.

Further information on possible repeated organ toxicity, reproductive toxicity and endocrine disrupting properties will be obtained from the not yet available Extended One Generation Toxicity Study (EOGRTS, rats, oral route) with cohort 1A (reproductive toxicity), cohort 1B (reproductive toxicity) without extension to mate the cohort 1B animals to produce the F2 generation and cohort 3 (developmental immunotoxicity) (see also section 7.10.).

7.9.5. Mutagenicity

BCPS has been evaluated in a battery of in vitro genotoxicity studies comprising in vitro gene mutation assays in bacterial cells, in vitro gene mutation assays in mammalian cells and in vitro chromosome aberration and sister chromatide exchange assays. Furthermore, BCPS has been tested in vivo in two mouse erythrocyte micronucleus assays and a rat liver unscheduled DNA synthesis (UDS) test.

A summary of the in vitro and in vivo tests as well as results and reliability scores are shown in Table 21.

Table 21 Summary of genotoxicity studies (standard information requirements): in vitro results and in vivo results

Test system / Study	Concentration range or dose levels tested	Results		Reference/ Remarks
In vitro tests				
		+ S9	**- S9**	NTP (2001)

Test system / Study	Concentration range or dose levels tested	Results	Reference/ Remarks
bacterial reverse mutation test (gene mutation assay) S. typhimurium (strains TA 1535, TA 97, TA 98 and TA 100 with and without metabolic activity) Test material: BCPS standard NTP study protocol similar to OECD TG 471	Test concentrations: 0, 0, 10, 33, 100, 333, and 1000 µg/plate Negative and positive controls included	+S9/-S9: negative	Klimisch 2 Key study - no cytotoxicity, but tested up to precipitating concentrations - only 4 strains tested
bacterial reverse mutation test (gene mutation assay) S. typhimurium (strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 with and without metabolic activation) Test material: BCPS Solvent: DMSO according to Ames (1975), minor modifications similar to OECD TG 471	0, 1.6, 8, 40, 200, 1000, 5000 µg/plate Negative and positive controls included	+ S9/- S9: negative	Unpublished study report (1982) GLP study in accordance with generally accepted scientific standards Klimisch 2 Supportive study - precipitation was observed at the highest dose 5 mg per plate - strains slightly different from OECD TG 471 - well documented study report

Test system / Study	Concentration range or dose levels tested	Results	Reference/ Remarks
mammalian cell gene mutation assay (gene mutation) Chinese hamster Ovary (CHO) CHO/HGPRT Test material: BCPS Purity: 99+%, Solvent: DMSO Treatment time: 5hrs with/without metabolic activation equivalent or similar to OECD TG 476 (in vitro mammalian cell gene mutation test)	Test concentrations: Initial assay: 134, 267, 534, 1069, 2137 µg/ml Confirmatory assay: 158, 316, 631, 1263, 2525 µg/ml and Negative control: solvent Positive control: ethylmethane-sulphonate (-S9 assay) benzo(a)pyrene: (+S9 assays):	+ S9/- S9: negative	Unpublished study report (1991a) Klimisch 1 GLP - all acceptability criteria fulfilled - highest test concentration above 2 mg/ml, no cytotoxicity observed - valid negative and positive controls
mammalian cell gene mutation assay (gene mutation) mouse lymphoma L5178Y cells Test material: BCPS Purity: not provided Solvent: DMSO Treatment time: 6 hrs with/without metabolic activation equivalent to OECD TG 490 (in vitro mammalian cell gene mutation tests using the thymidine kinase gene), former OECD TG 476	Test concentrations: 10, 20, 40, 80, and 160 µg/ml Positive control substance(s): ethylmethane-sulphonate (EMS) (-S9) 3-methylcholanthrene (3-MC) (+S9) Cytotoxicity: yes, at highest dose between 10-20% relative total growth	Negative with metabolic activation; Equivocal mutagenic response without metabolic activation (according to applicants equivocal mutagenic without metabolic activation)	Unpublished study report (1994) GLP Klimisch 1 - cytotoxicity has been defined by relative total growth (RTG) - top dose selection appropriate - valid positive and negative control - 6 hrs treatment (prolonged exposure time: enhancement of cytotoxicity)

Test system / Study	Concentration range or dose levels tested	Results	Reference/ Remarks
in vitro mammalian chromosome aberration test (chromosome aberration) Chinese hamster Ovary (CHO) cells Test material: BCPS Purity: >99% Solvent: DMSO Treatment time: +S9: 2 hrs –S9: 13.5 hrs NTP standard protocol equivalent or similar to OECD TG 473 (in vitro mammalian chromosome aberration test)	-S9: 94, 201, 432 µg/ml +S9 Trial 1: 9.4, 20, 930, 2000 µg/ml +S9 Trial 2: 750, 1000, 1250, 1500, 2000 µg/ml Positive control substance(s):cyclo-phosphamide (+S9), mitomycin C (-S9) Cytotoxicity: yes (highest dose was limited by cytotoxicity)	+S9/-S9: negative	NTP (2001) Klimisch 2 Key study - NTP report, no original study report, no detail study description - no detailed information on negative and positive controls, cell proliferation, cytotoxicity - 2 hrs treatment with S9 (vs. 3- 6 hrs OECD TG re-commendation) - 200 instead of 300 metaphases were investigated per concentration

Test system / Study	Concentration range or dose levels tested	Results	Reference/ Remarks
sister chromatid exchange assay in mammalian cells (chromosome aberration) Chinese hamster Ovary (CHO) cells Test material: BCPS Purity: >99% Solvent: DMSO Incubation time: +S9: 2 hrs –S9: first assay: 26 hrs, second assay: 33 hrs NTP standard protocol equivalent or similar to OECDTG 479 (genetic toxicology: in vitro sister chromatid exchange); OECD TG has been deleted in 2014	+S9: 6.7, 20, 667, 2000 µg/ml -S9 first assay: 20, 67, 200, 667 µg/ml -S9 second assay: 200, 250, 300µg/ml Positive control substance(s):cyclo-phosphamide (+S9), mitomycin C (-S9) Cytotoxicity: yes (at 667 µg/ml, -S9)	+S9: negative -S9: equivocal	NTP (2001) Klimisch 2 - OECD TG 479 has been deleted since there is a lack of understanding of the mechanisms of action detected by the test - NTP report, no original study report, no detail study description - 50 second-division metaphase (according TG at least 25) - positive result: 20% above concurrent control, equivocal: although not 20% above concurrent control statistically significant

Test system / Study	Concentration range or dose levels tested	Results	Reference/ Remarks
micronucleus assay (chromosome aberration) Test species: mouse (B6C3F1)(m) Test material: BCPS; Vehicle: corn oil Application route: intraperitoneal injecton NTP standard protocol according to Shelby MD et al. (1993) equivalent or similar to OECD TG 474 (mammalian erythrocyte micro-nucleus test)	200, 400, 600, and 800 mg/kg bw (actual injected) treatment three times at 24-hour intervals Positive control substance: cyclophosphamide	Equivocal (slight but statistically significant increase in micro-nucleated poly-chromatic erythrocytes)	NTP (2001) 2 (reliable with restrictions) key study experimental result - NTP report, no original study report, no detail study description - no information on preliminary range finding studies - 2000 polychromatic erythrocytes instead of 4000/ animal were scored
micronucleus assay (chromosome aberration) Test species: mouse (ICR) (m/f) Test material: BCPS Vehicle: Corn oil Application route: intraperitoneal injection, single application equivalent or similar to OECD TG 474 (mammalian erythrocyte micro-nucleus test)	Dose levels: 196, 980 and 1960 mg/kg bw (actual injected) Positive control substance(s): triethylenemelamine Tested up to 80% of LD_{50}; preliminary toxicity tests	Evaluation of results: negative	Unpublished study report (1991b) GLP Klimisch 2 (reliable with restrictions) supporting study - 1000 polychromatic erythrocytes instead of 4000/ animal were analysed

DNA damage and/or repair (unscheduled DNA synthesis - UDS) Test species: Sprague-Dawley rat (m) Test material: BCPS, Purity: 99.1%; Vehicle: Aqueous 1% w/v methyl cellulose Application route: oral, gavage Sampling time: 2 hrs, 14 hrs according OECD TG 486 (unscheduled DNA synthesis test with mammalian liver cells in vivo)	600 and 2000 mg/kg bw	Negative No increase in nuclear grains	Unpublished study report (2000) GLP Klimisch 2 supporting study - preliminary toxicity test - three cultures per animal - 50 hepatocytes were analysed (100 cells according to OECD TG 486)

In vitro mutagenicity

BCPS does not induce gene mutations in bacterial gene mutation assays (NTP, 2001, Unpublished study report, 1982), either in the presence or absence of a mammalian metabolic activation system.

BCPS was tested in the CHO/HGPRT mutation assay in the absence and presence of S9 using a protocol comparable to the OECD TG 476 standards (Unpublished study report, 1991a). The test concentration applied was > 2 mg/ml. The test item was tested beyond it´s limit of solubility under culture conditions. At two test concentrations the mutant frequency was above 20 mutants per 10^6 clonable cells (indicator for positive response). Nevertheless, no dose-response relationship was seen and the result was not confirmed in the confirmatory assay. BCPS did not cause gene mutation in this test system both in the absence and presence of metabolic activation.

In the unpublished study report (1994) the results of mouse lymphoma L5178Y assay carried out with BCPS at dose levels of 10, 20, 40, 80 and 160 µg/ml both, in the presence and absence of metabolic activation system were reported. Precipitation of the test material was evident at concentrations ≥ 80 µg/ml BCPS. Concentration dependent cytotoxicity was demonstrated in all assays in absence and presence of S9. In order to reach critical levels of toxicity the exposure period was expanded from 4 to 6 hour treatment. The results of experiments in the presence of S9 were negative. The mutation frequency (MF) in all cultures was less than 90 x 10^{-6} (= Global evaluation factor (GEF)) above concurrent control level, which is the criterion for a positive response according to OECD TG 490.

In the absence of metabolic activation, equivocal mutagenic response has been obtained. Data indicate that at BCPS concentrations of 40 and 160 µg/ml in the first assay and 160 µg/ml in the second assay the GEF was exceeded and the increase was concentration related. According to the study authors a weak mutagenic activity is indicated by these results. Nevertheless, the increase in MF was accompanied by cytotoxicity (22 % relative

total growth (RTG) at 40 µg/ml (first assay) and 20 % RTG at 160 µg/ml (first and second assay)). According to OECD TG 490 special care should be taken, when interpreting test results occurring only between 10-20% RTG (USF DA, 2012). Positive results in this assay have been obtained at 20 % RTG or slightly above. Correlation analysis reveals that cytotoxicity has a high impact on the MF. eMSCA agrees that there is an equivocal response in the absence of S9 applying lately recommended evaluation criteria cited in the OECD TG 490 (2016).

In the chromosome aberration test (NTP, 2001) according to OECD TG 473 Chinese Hamster Ovary (CHO) cells were incubated with BCPS in the presence or absence of metabolic activation (S9). The test compound was tested at concentrations of 94, 201, 432 µg/ml without metabolic activation and at concentrations of 9.4, 20, 930, 2000 µg/ml with metabolic activation. The highest concentration was cytotoxic. A statistically significantly increased chromosomal aberration rate of 3.5% was only seen at 930 µg/ml in the presence of metabolic activation. In a second test with metabolic activation using BCPS concentrations of up to 2000 µg/ml no increased number of chromosomal aberrations was found, which indicates that the isolated finding at 930 µg/ml in the first test was without biological relevance. In conclusion, BCPS did not induce chromosomal aberrations in CHO cells with or without metabolic activation system.

A sister chromatid exchange (SCE) assay according to OECD TG 479 was performed with BCPS with and without metabolic activation (S9) (NTP, 2001). BCPS in presence of metabolic activation was tested in a concentration range of up to 2000 µg/ml and did not reveal positive results. In the assays without metabolic activation BCPS was tested up to 300 µg/ml. Dose-related effects were obtained in the first trail over a concentration range of 20 to 200 µg/ml (treatment time: 26 hrs). The SCE frequency was not 20% above the concurrent solvent but were statistically significant increased. Therefore the effects are considered equivocal. In the second trial (longer incubation time) without S9 mix a slightly but not significant increase was detected. NTP experts give more weight to the first trial, since a broader range of concentrations was tested and cells are shorter exposed to BrdU and consider the results as equivocal. The registrants, in contrast, consider the SCE results without S9 test as negative, since the SCE frequency increase was below 20% compared to the concurrent control and the second trail, which was designed to clarify the equivocal results of the first trial, was negative.

eMSCA considers the SCE results without metabolic activation in line with NTP experts as equivocal, since also the second trail indicate although not statistical significant a dose-dependent increase in SCEs ($p=0.008$) and the first trail clearly does indicate a statistical significant increase in SCEs ($p=0.004$).

In conclusion BCPS is not mutagenic in bacteria mutation assays. Equivocal mutagenic activity were observed in a reliable mouse lymphoma assay and in a sister chromatide assay without metabolic activation. The SCE results are considered negative with metabolic activation system and equivocal without metabolic activation system. The in vitro chromosome aberration test with CHO cells is negative.

Based on the data set it is not unambiguously clarified if BCPS does provoke mutagenic activity in vitro. The eMSCA concludes that the mutagenic activity in vitro is equivocal.

In vivo mutagenicity

Data on in vivo mutagenicity is available from two mouse erythrocyte micronucleus assays (NTP 2001, Unpublished study report 1991b) and a rat liver unscheduled DNA synthesis (UDS) test (Unpublished study report, 2000).

In the micronucleus study by NTP (2001 published, but performed 1995-1997) groups of 5 males B6C3F1 mice were exposed three times every 24 h to BCPS doses of 200, 400, 600, and 800 mg/kg bw (intraperitoneal injection). Analyses were performed 24 hrs after the last dosing. In the first trial the frequency of micronucleated polychromatic

erythrocytes (PCE) was increased in the 400 mg/kg/d group only (3.8 ± 1.29 micronucleated PCEs/1000 PCEs), in the second trial a significant increase was seen in the 400 and 800 mg/kg/d (3.25 ± 1.05 and 3.30 ± 0.44 microucleated PCEs/1000 PCEs, respectively) groups. A clear dose-response relationship (trend analysis, p≤0.007) was established in the second trail.

The overall conclusion in the NTP report is that BCPS gave a positive response in the micronucleus test in vivo. The experts took into consideration the results of statistical analysis, reproducibility of effects and the magnitude of the effects.It is not indicated in the NTP report if historical control data have been considered for drawing the conclusion.

The registrants provided a publication, Shelby MD et al. (1993), in which more than 80 datasets from NTP contracted laboratories using the three day exposure study protocol are provided to analyse the historical control data. In this study the micronuclei fraction in corn oil treated B6C3F1 control mice ranged from 1.1 to 3.7 (outlier at 4.6) and therefore, the observed positive results of BCPS treated mice are within or close to the range of control data.

Taking into account the historical control data it is questionable if the observed positive outcome with BCPS are of biological significance (NTP, 2001). The eMSCA considers the outcome of the micronucleus assays as equivocal.

A second mouse erythrocyte micronucleus test (GLP and guideline conform) reported by Unpublished study report (1991b) was negative. In that study BCPS was administered once intra peritoneal to groups of 5 males and 5 female ICR mice at concentrations of 196, 980, and 1960 mg/kg bw. The high dose level was calculated to be 80% of the LD50 and caused clinical signs of toxicity. Concurrent vehicle (corn oil) and positive control groups were included. Bone marrow cells were prepared 24hrs, 48hrs, and 72hrs after exposure and analysed for micronucleated PCEs. There was no statistically significant increase in the micronucleus frequency in comparison to controls. The test is therefore negative.

The unscheduled DNA synthesis test (GLP, guideline conform) was assessed in hepatocytes following acute oral administration of 600 and 2000 mg/kg bw BCPS. The test did not cause any significant increase in the nuclear grain count (measure for DNA repair) at any point, indicating that BCPS does not induce DNA damage in rat liver under this test condition.

Conclusion

The eMSCA considers the *in vitro* mutagenicity data as inconclusive. There is some equivocal evidence that mutagenic activity was present in the mouse lymphoma assay and in the sister chromatid assay without metabolic activation. Bacterial gene mutation assays and Chinese hamster ovary cell assays (gene mutation and chromosome aberration) are negative.

Equivocal *in vivo* mutagenic activity was observed in a mammalian erythrocyte micronucleus test. In contrast no mutagenic activity was observed in a second mammalian erythrocyte micronucleus test. The unscheduled DNA synthesis (UDS) test did not demonstrate any positive response.

It is noted that the carcinogenicity studies (see chapter 7.9.6) do not indicate any carcinogenic response. However, the applied doses in the carcinogenicity studies might have been too low to properly assess BCPS's potential to induce neoplastic effects (low statistical power).

According to CLP guidance on application of CLP criteria[18] a classification for germ cell mutagenicity is warranted if there are positive results in at least one valid *in vivo* mutagenicity study, including tests with intraperitoneal application.

Overall, the eMSCA concludes that there is not sufficient evidence to support a classification of the substance for Muta. Cat. 2. Further animal testing is not proposed, taking into account that overall there is a rather low concern for mutagenic activity.

7.9.6. Carcinogenicity

Experimental evidence for carcinogenicity submitted by the registrant is provided in table 22.

Table 22 Studies on carcinogenicity with BCPS

Study/Method	Results	Remarks/ Reference
Carcinogenicity study Test species: rat (Fischer 344) male/female Number of animals: 50/sex/dose Test material: BCPS Purity: >99% Vehicle: no vehicle Application route: oral (feed) 0, 10, 30 or 100 ppm (males) (corresponding to 0, 0.5, 1.5 and 5.0 mg/kg bw/d) 0, 30, 100, or 300 ppm (females)(corresponding to 0, 1.6, 5.4 and 17 mg/kg bw/d) Exposure: 105 to 106 weeks equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies)	No carcinogenic effects NOAEL (carcinogenicity): > 5 mg/kg bw/day for males NOAEL (carcinogenicity): > 17 mg/kg bw/day for females NOAEL (repeated dose): 1.5 mg/kg bw/day (bile duct hyperplasia and centrilobular degeneration noted in females at 5.4 mg/kg bw, for males/females hepatocyte hypertrophy noted at 5/5.4 mg/kg bw/day)	NTP (2001) 1 (reliable without restriction) GLP key study experimental result - 20 animals (10 m, 10 f) were treated for up to 18 month with BCPS to determine BCPS plasma concentration; time-point: 2wks, 3, 12, 18 month - no haematology or clinical biochemistry - dose selection based on outcome of 14 weeks study
Carcinogenicity study Test species: mouse (B6C3F1) male/female Number of animals: 50/sex/route	No carcinogenic effects NOAEL (carcinogenicity): > 40 mg/kg bw/day for males NOAEL (carcinogenicity): > 33 mg/kg bw/d for females	NTP (2001) 1 (reliable without restriction) GLP key study

[18] ECHA (2017). Guidance on the application of the CLP criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 5.0

Study/Method	Results	Remarks/ Reference
Test material: BCPS Purity: > 99% Vehicle: no vehicle Application route: oral (feed) 0, 30, 100 or 300 ppm (males and females) corresponding to 0, 4, 13 or 40 mg/kg bw/d (males) 0, 3, 10 and 33 mg/kg bw/d Exposure: 105 to 106 weeks equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies)	NOEL (repeated dose): 3 mg/kg bw/d (based on centrilobular hepatocyte hypertrophy noted in female rats at 13 mg/kg bw/d); no NOEL for males identified (≤ 4 mg/kg bw/d) NOAEL (repeated dose): 10 mg/kg bw/d (based on eosinophilic foci (female)	experimental result - 20 animals (10 m, 10 f were treated for up to 12 month for BCPS plasma determination, time-point: 2wks, 3, and 12 month - no haematology or clinical chemistry - dose selection based on outcome of 14 weeks study (body and organ weight, liver effects)

In the carcinogenicity study carried out with Fischer 344 rats (NTP, 2001) BCPS was administered via the diet for a period of two years to 50 animals/sex/dose. Male rats were exposed to 0, 0.5, 1.5 or 5.0 mg/kg bw/d and female rats to 0, 1.6, 5.4 or 17 mg/kg bw/d BCPS. In addition three animals per sex and dose were used for BCPS plasma level determination at 2 weeks and 3, 12 and 18 months. BCPS treatment had no effect on survival rates, induced no clinical signs of toxicity, and resulted in no changes in food consumption or gross lesions attributable to BCPS.

Mean body weights in males (1.5 and 5 mg/kg bw/d) were only slightly reduced during the latter part of the study. The mean body weights of female rats in the highest dose group (17 mg/kg bw/d) were lower at the end of the study (88% of the controls). Incidences of centrilobular hepatocyte hypertrophy in the highest dose groups (5.0 mg/kg bw/d male and 5.4 and 17 mg/kg bw/d female rats) were significantly greater than those in the controls. In addition, the incidences of bile duct hyperplasia and centrilobular degeneration were also significantly increased in 5.4 and 17 mg/kg bw/d females. Plasma concentrations were slightly higher in females than in males after 12 and 18 months. Samples showed a correlation between exposure concentration and plasma BCPS concentration.

The incidences of malignant mesothelioma in the 1.5 and 5 mg/kg bw/d group were slightly but not statistically increased (0 mg/kg bw/d: 2/50, 0.5 mg/kg bw/d: 2/50, 1.5 mg/kg bw/d: 5/50, 5 mg/kg bw/d: 6/50). Although the increase was not statistically significant, leaving doubts on whether it was exposure related, it is notable that the values exceeded historical control values. The malignant mesothelioma resulted from the tunica vaginalis covering the testes and the epididymis. Furthermore, a significant reduction in pituitary gland adenoma was observed in female rats exposed to 1.6 and 17 mg/kg bw/d, however without dose relationship. In conclusion, there are no neoplastic changes in rats apparently attributable to BCPS exposure.

In the corresponding carcinogenicity study mice (B6C3F1, 50 animals/sex/dose) were exposed to BCPS via the diet for 105 to 106 weeks. Male mice were exposed to 0, 4, 13 or 40 mg/kg bw/d and female mice to 0, 3, 10 or 33 mg/kg bw/d. In addition three animals per sex and dose were used for BCPS plasma level determination at 2 weeks, 3 month and 12 months. Mean body weights in the highest dose group (40 mg/kg bw/d males, 33 mg/kg bw/d females) were less than those of the controls throughout the study. Females in the

highest dose group had a reduced body weight of 11% compared to the control group at the latter period of the study. BCPS exposure resulted in no treatment related changes of mortality rates, clinical signs, food consumption and macroscopical findings. There were no increases in the incidences of neoplasms in the liver or any other organ. The higher incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in the 3 mg/kg bw/d females was greater than in the controls, but not dose related and within the historical control ranges. For male mice there was a negative trend in the incidence of alveolar/bronchiolar adenoma or carcinoma.

The incidences of centrilobular hepatocyte hypertrophy in all exposed groups of male mice and in 10 and 33 mg/kg bw/d females were significantly greater than those in the controls. The incidence of eosinophilic foci in 33 mg/kg bw/d females was significantly increased. Plasma concentrations were higher in females than in males and correlate with the exposure concentrations. It is stated in the NTP report that dose-dependent increases in the incidences of eosinophilic foci in the liver of female mice, along with the ability of p,pN-dichlorodiphenyl sulfone to cause microsomal enzyme induction and hepatomegaly, are consistent with activity of the chemical as a weak hepatic tumour promoter. Adverse effects may possibly arise from increased mixed-function oxidase activities that cause altered sensitivities towards hepatotoxins or hepatocarcinogens.

Dose selection is key in chronic and carcinogenicity studies. It is questionable if the maximal tolerable dose (MTD) has been reached for male animals (rats and mice). Only in female animals the body weight reduction was more than 10% in the highest dose group at the end of the study irrespective of food consumption, which is indicative for systemic toxic effects. It is concluded that, only mild toxic effects were reached at the highest dose level and a MTD especially for the male animals has not been reached which questions the reliability of the carcinogenicity studies. However, the studies have been carried out under GLP and are guideline conform, except for the dose selection.

Conclusion

The eMSCA concludes that no carcinogenic effects attributable to BCPS application were observed in the available data. There are some remaining uncertainties since there is some evidence that BCPS has mutagenic properties and the applied doses in the carcinogenicity studies are possibly too low to properly assess the carcinogenic potential of BCPS.

Based on the available information no classification for carcinogenicity according to CLP Regulation 1272/2008/EC is proposed.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

A Reproduction/Developmental Toxicity Screening Test (OECD TG 421) and a Prenatal Developmental Toxicity Study (OECD TG 414) are available. Moreover, additional information from repeated dose toxicity studies is considered.

According to REACH Annex X an Extended one-generation reproductive toxicity study (EOGRTS) is standard data requirement for substances manufactured and imported in quantities of 1000 tons or more. As indicated in section 2, a testing proposal Decision, requesting provision of an EOGRTS by 06 August 2021, was notified to the Registrant(s).

Table 23 Studies on fertility

Study/Method	Results	Remarks/ Reference
Screening test Test species: rat (Sprague-Dawley)	NOAEL (for adult toxicity) (P): 15 mg/kg bw/d (male) based on centrilobular hypertrophy associated with centrilobular hepatocyte	Unpublished study report (2008) GLP Klimisch 1

Study/Method	Results	Remarks/ Reference
Number of animals:10/sex/group (male/female) Test material: BCPS Purity: ≥98.4% Vehicle: arachis oil Application route: oral (gavage) 0, 5, 15, and 50 mg/kg bw/d Exposure: 54 days (including a two week maturation phase, pairing, gestation and early lactation for females) (once daily) according to OECD TG 421 (Reproduction/Develop-mental Toxicity Screening Test)	enlargement (degenerative type of change) NOAEL (toxicity to fertility) (P): 50 mg/kg bw/d no effects on reproductive performance up to and including the high dose level Significant increase in relative testes and epididymides weights at the highest dose level. NOAEL (developmental toxicity): 15 mg/kg bw/d (reduction in bw gain was evident in off-spring)	Key study - Test conducted prior to OECD TG update to include endocrine disruptor relevant endpoints - no angiogenital distance measurement or nipple retention in male pups, no thyroid hormone analysis - no weight measurement of prostate and seminal vesicles - number of females only 10/group not as recommended in TG (n=12-13 females)

Effects on fertility

In a reproduction/developmental toxicity screening study (according to OECD TG 421) BCPS was applied by gavage at dose levels of 5, 15, 50 mg/kg bw/day. Males in the highest dose group (50 mg/kg bw/d) showed a reduction in cumulative body weight gain throughout the treatment period and a reduction in weekly body weight gain during the first two weeks of treatment. BCPS treatment resulted in centrilobular hepatocyte enlargement in all animals. The incidence was significant for all treatment groups. Liver weight (absolute and relative) was increased in all groups. Liver enlargement was present at the 50 mg/kg bw/d group (males and females). The NOAEL for parent animals is set at 15 mg/kg bw/d based on centrilobular heapatocyte vacuolation seen at 50 mg/kg/day which is considered as a degenerative type of change. In the study no effects on the reproductive performance (mating, gestation length) was observed. The application of BCPS had no effect on offspring litter size and viability. But, at the highest concentration a reduced bodyweight gain was observed in off-spring between day 1 and 4. Thus a NOAEL for developmental toxicity was set at 15 mg/kg bw/d.

In this study males treated with 50 mg/kg bw/d showed a significant increase in relative testes and epididymidis weight. No histological correlates were found. The change was characterized by 18% increase for relative testis weight ($p<0.01$) and 14% increase for relative epididymidis weight ($p<0.001$). Increased epididymidis weight can be an indication for androgenicity.

During the 14 weeks and 2 year oral repeated dose toxicity studies (described in more detail in section 7.9.4) with rats and mice also reproductive organs were studied, with regard to organ weights, gross lesions and histological examinations. The following organs were examined: ovary, preputial gland, prostate gland, testis (with epididymis and seminal vehicle) and uterus.

During the 14 week study in rats the relative testis (right) weight was significantly increased from a dose level of 19 mg/kg bw onwards and in mice in the two highest groups

(15 and 50 mg/kg bw/day group). In the rat study also the absolute testis weight was increased at the highest dose levels. In the 14 week study with mice also a significant relative weight increase of ovaries at dose levels of 50, 165 and 480 mg/kg bw/d and a relative weight increase of uterus at the two highest dose levels was observed. No histopathological correlates were found.

Based on the limited information which can be obtained from the available screening study it cannot be concluded whether BCPS has any impact on fertility. Based on the available data no classification for reproductive effects - fertility - is proposed by eMSCA.

Table 24 Studies on developmental toxicity

Study/Method	Results	Remarks/ Reference
Test species: rat (Wistar) Number of animals: 25/group Test material: BCPS Purity: 99.8% Vehicle: carboxymethyl-cellulose (CMC) (1% in drinking water) Application route: oral-gavage 0, 20, 60 and 180 mg/kg bw/d Exposure: 14 days between GD 6 and GD 19 (once daily by oral gavage) according to OECD TG 414 (Prenatal Developmental Toxicity Study)	NOAEL (maternal toxicity):60 mg/kg bw/d (stat. significant reduction in food intake and corrected (net) body weight gain in the high dose group of 180 mg/kg bw/d) NOAEL (developmental toxicity): 180 mg/kg/d (no adverse developmental effects were observed)	Unpublished study report (2014) Klimisch 1 GLP -Test conducted prior to OECD TG update to include endocrine disruptor relevant endpoints (no AGD measurement, no thyroid hormone analysis) - To cover the full organogenesis exposure should start on GD 5, for a bioaccumulating substance an earlier start of treatment might also be considered
Screening test Test species: rat (Sprague-Dawley) Number of animals: 10/sex/group (male/female) Test material: BCPS Purity: ≥98.4% Vehicle: arachis oil Application route: oral (gavage) 0, 5, 15, and 50 mg/kg bw/d Exposure: 54 days (including a two week maturation phase, pairing, gestation and early lactation for females) (once daily)	NOAEL (for adult toxicity) (P): 15 mg/kg bw/day (male) based on centrilobular hypertrophy associated with centrilobular hepatocyte enlargement (degenerative type of change) NOAEL (toxicity to fertility) (P): 50 mg/kg bw/d no effects on reproductive performance up to and including the high dose level Significant increase in relative testes and epididymides weights at the highest dose level. NOAEL (developmental toxicity): 15 mg/kg bw/d	Unpublished study report (2008) Klimisch 1 GLP Key study - Test conducted prior to OECD TG update to include endocrine disruptor relevant endpoints - no AGD measurement or nipple retention in male pups, no thyroid hormone analysis - no weight measurement of

according to OECD TG 421 (Reproduction/Developmental Toxicity Screening Test)	(reduction in bw gain was evident in off-springs)	prostate and seminal vesicles - number of females only 10/group not as recommended in TG (n=12-13 females)

Effects on development

The developmental toxicity of BCPS was investigated in rats according to OECD TG 414 (prenatal developmental toxicity study) and according to OECD TG 421 (Reproduction/ Developmental Toxicity Screening Test).

In the GLP and guideline conform (OECD TG 414) prenatal developmental toxicity study BCPS was applied orally to Wistar rats at doses of 20, 60 and 180 mg/kg bw/d during GD 6 -19. The dams were sacrificed on GD 20 and foetal development was assessed. Animals in the high dose group (180 mg/kg bw/d) showed decreased food consumption and decreased net body weight gain ($p<0.05$). No effects were observed on survival or gestational parameters. There were no adverse effects observed among foetuses either in soft tissue or skeletal malformations or variations related to BCPS administration. The NOAEL for maternal toxicity is 60 mg/kg bw/d, and the NOAEL for prenatal developmental toxicity is ≥ 180 mg/kg bw/d.

In the Reproduction/Developmental screening study BCPS was administered orally to Sprague-Dawley rats at dose levels of 5, 15, 50 mg/kg bw/d. At the highest concentration a reduced bodyweight gain was observed in off-springs between day 1 and 4. Thus, a NOAEL for developmental toxicity was set at 15 mg/kg bw/d.

Conclusion

According to REACH Annex X of the REACH Regulation, an EOGRTS is standard data requirement for substances manufactured and imported in quantities of 1000 tons or more. The registrants are requested according to the decision on testing proposal to carry out an EOGRTS (rats, oral route) with cohort 1A (reproductive toxicity), cohort 1B (reproductive toxicity) without extension to mate the cohort 1B animals to produce the F2 generation and cohort 3 (developmental immunotoxicity).

To draw a firm conclusion on reproductive toxicity the results of the EOGRTS study need to be considered. Based on the available data no classification for reproductive effects is proposed by eMSCA at this time.

7.9.8. Hazard assessment of physico-chemical properties

No need for clarification of potentially relevant concerns was identified.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Not evaluated.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

BCPS has no acute toxic potential. The substance does not possess skin irritation potential, whereas the classification criteriea according to CLP Regulation (EC) No 1272/2008 for Eye

Irrit. Cat. 2 are fulfilled. No harmonsided classification is proposed at the moment. The substance does not possess any sensitisation potential.

BCPS is slowly metabolised and distributed to tissues (especially to adipose tissue). A long elimination half-life in the adipose tissue after single exposure might be indicative for a bioaccumulation potential.

Liver is the main target organ affected through BCPS exposure in rodents. The liver weights are increased and the effects are mostly characterised by centrilobular hypertrophy. These observations are most possibly related to liver enzyme induction of drug metabolizing enzymes, which is considered an adaptive process.

Overall, the eMSCA concludes that there is insufficient evidence to support a classification of the substance for Muta. Cat. 2 according to CLP Regulation No 1272/2008/EC. The available carcinogenicity studies in mice and rats do not indicate any neoplastic effects attributable to BCPS application, but doses applied in these two studies seem to be too low to fully assess whether BCPS has a carcinogenic potential.

Based on the available data no classification is proposed for reproduction. There is evidence that BCPS has an impact on the integrity of testes and epididymides and also female reproductive organs appeared affected. Nevertheless, for this endpoint REACH Annex X requirements are not covered by present available data. An EOGRTS study is pending and will be submitted by registrants.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

See 7.10.3

7.10.2. Endocrine disruption - Human health

See 7.10.3

7.10.3. Conclusion on endocrine disrupting properties (combined)

As the available data indicating a potential for endocrine disruption are relevant for both human health and environment, the assessment of these data is provided together below.

An assessment of the available data indicates that BCPS can interfere with signalling via the (anti)androgenic, (anti)-estrogenic and/or thyroid pathway.

(Anti-)androgenic and (anti-)estrogenic activity

(Anti-)androgenic as well as anti-estrogenic activity was seen in several ToxCast assays[19]: Data regarding androgen axis indicate that the registered substance has antiandrogenic activity, although the ToxCast Pathway Model (AUC), the COMPARA (Consensus) and the CERAPP Potency Level (Consensus) were negative for (anti-) androgenic activity as well as (anti-)estrogenic activity. In the CERAPP Potency Level (From Literature) a very weak binding to the estrogen receptor is reported.

The following tests relevant for the (anti-)androgenic or anti-estrogenic pathway were positive:

- TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_R1881: AC_{50} of 20.96

[19] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=80-07-9 (visited on 10.3.2020)

- TOX21_AR_LUC_MDAKB2_Antagonist_10nM_R1881: AC_{50} of 79.61 (Flag: Only highest concentration above baseline, active)
- TOX21_AR_BLA_Antagonist_ratio: AC_{50} of 107.04 (Flag: Less than 50% efficacy)
- OT_AR_ARELUC_AG_1440: AC_{50} of 0.17 (Flags: AC_{50} less than lowest concentration tested, noisy data)
- TOX21_ERa_LUC_VM7_Antagonist_0.1nM_E2: AC_{50} of 64.53 (Flag: Less than 50% efficacy)
- TOX21_ERa_LUC_VM7_Antagonist_0.5nM_E2: AC_{50} of 72.72 (Flag: Less than 50% efficacy)
- TOX21_ERR_Antagonist: AC_{50} of 35.94
- TOX21_ERb_BLA_Antagonist_ratio: AC_{50} of 52.40 (Flag: Less than 50% efficacy)

The cytotoxicity limit was at 19.37.

Kleinstreuer et al. (2017) chose for their development and validation of a computational model for androgen receptor activity an in vitro battery of 11 androgen pathway assays plus one antagonist confirmation assay using a higher concentration of the activating ligand to characterise competitive binding (TOX21_AR_LUC_MDAKB2_Antagonist). The initial Tox21_MDAKB2_Luc_Antagonist assay run with a stimulatory methyltrienolone concentration of 10 nM predominately only identified the strong antagonists that could compete with the high agonist concentration. When the assay was run with 0.5 nM, more of the weak antagonists were identified. The shift in potency between the two conditions was useful for identifying indirect inhibitors of the assay signal.

According to Kleinstreuer et al. substances positive in these tests but not active in the co-regulator recruitment assays and/or binding assays are predicted to act via the interference pathway suppression of protein binding - for the registered substance the co-regulator recruitment assays are negative, while for the binding assays no data are available. Nevertheless, in the discussion of Kleinstreuer et al. (2017) it is stated that for substances with a clear shift in the confirmation assay data (data from Tox21_AR_LUC_MDAKB2_Antagonist assays) this may be sufficient evidence of AR-mediated activity, regardless of model score, as some antagonists may bind outside the ligand binding domain, otherwise block dimerization, or act on some later step in the pathway. Chemicals with this type of response were identified and prioritized by the activity confidence scoring system.

For the registered substance this shift in potency in the correct direction was observed, indicating antiandrogenic activity. The observed potential for antiandrogenic activity remains valid, although data from another older in vitro test provide a negative result: In an androgen reporter assay the substance screened negative in a Chinese hamster ovarian cell line (CHO K1) stably expressing the human androgen receptor (Roy et al., 2004).

Regarding estrogenicity Yang et al. (2011) state that polyethersulfone hard & clear products (with monomers of the registered substance and 1,4 dihydroxybenzene) consistently released chemicals having estrogenic or anti-estrogenic activity, especially when stressed with UV light, possibly from unreacted phenolic monomer residues or phenolic stress-degradation products. No substance specific data are available.

Although Ng et al. (2015) predicted BPCS as nonestrogenic using their in silico model, this is not in contradiction to the publication of Yang et al. (2011) as the authors speculate that metabolites of sulphon may be estrogenic. As another explanation for the very weak, equivocal nature of the estrogenic activity of sulphon, it is mentioned that the ER binding score (−6.544) of sulphon is very close to the model cutoff for a binder (−6.612).

Also in vivo data provide evidence for the potential to act via the estrogen, androgen or steroidogenesis pathway:

During the 14 weeks and 2 year oral repeated dose toxicity studies and reproductive toxicity studies (described in more detail in repeated dose and reproductive toxicity sections) with rats and mice reproductive organs were studied with regard to organ weights, gross lesions and histological examinations (see below). In order to put the effects on reproductive organ weights in relation to other effects also liver weight changes and body weight changes are described in the same section.

In the oral 14 week rat study (NTP, 2001) a statistically significant increase was observed at 19 mg/kg bw/d for relative testis weight (7.9%, $p<0.01$) and for the relative and absolute testis weight at 65 mg/kg bw/day (17.1% for relative weight, $p<0.01$, and 5.3% for absolute weight, $p<0.05$) and 200 mg/kg bw/d (30% for relative weight, $p<0.01$, and 3.4% for absolute weight, $p<0.05$). For body weight from 19 mg/kg bw/d onwards statistically significant decreases were observed: 5.2% at 19 mg/kg bw/d ($p\leq0.05$), 7.9% at 65 mg/kg bw/d ($p\leq0.01$) and 17.6% at 200 mg/kg bw/d ($p\leq0.01$). It is noteable, that already from 6 mg/kg bw/d onwards significant effects on absolute (17.2%, $p<0.01$) and relative liver weight (20.4%, $p<0.01$) were observed.

In the 14 week toxicity study in mice (NTP, 2001) also a significant increase of relative right testis weight was observed in the two highest dose groups (165 mg/kg bw/d: 9.2%, 480 mg/kg bw/d: 17.6 %, both $p\leq0.01$). At these dose levels statistically significant mean body weight reductions were observed: 14.2% and 15.2% (both $p\leq0.01$).

A significant testes weight increase was also observed in an OECD 421 test (Safepharm, 2008): At the highest dose (50 mg/kg bw/d) relative testes weight was increased by 18%, although a not significant increase in absolute and relative weight was seen at all dose levels. Males treated with 50 mg/kg bw/d showed a reduction in cumulative body weight gain throughout the treatment period and a reduction in weekly body weight gain during the first two weeks of treatment. No such effects were detected in animals treated with 15 or 5 mg/kg bw/d. The testis findings were without histological correlates. In this study also the weight of epididymides was increased: At the highest dose (50 mg/kg bw/day) relative epidymides weight was increased by 14%, although a not significant increase in absolute and relative weight was seen at all dose levels.

In the 14 week study significant changes of relative weight of hormone dependent organs in female mice are described (NTP, 2001): The relative weight of ovaries was significantly increased from 50 mg/kg bw/day onwards (16.9% at 50 mg/kg bw/day, 19.1% at 165 mg/kg bw/day and 13.5% at 480 mg/kg bw/day, all $p\leq0.05$). The relative weight of uterus was increased in the two highest dose groups (47% at 165 mg/kg bw/day and % at 480 mg/kg bw/day, both $p<0.01$). These organ weight changes were without histopathological correlate. From 50 mg/kg bw/day onwards mean body weight was reduced: -8.7% at 50 mg/kg bw/day, -13% at 165 mg/kg bw/day and -13.7% at 480 mg/kg bw/day. In the 14 week toxicity study in rats (NTP, 2001) ovaries and uterus weights were not changed.

No details on organ weights are provided for the 2 year carcinogenicity studies with mice and rats. In the 2 year carcinogenicity study carried out with rats the incidences of malignant mesothelioma in the 1.5 and 5 mg/kg bw/d group were slightly but not statistically significantly increased (0 mg/kg bw/d: 2/50, 0.5 mg/kg bw/d: 2/50, 1.5 mg/kg bw/d: 5/50, 5 mg/kg bw/d: 6/50). Although not significant it is notable that the values exceeded historical control values. The malignant mesothelioma resulted from the tunica vaginalis covering the testes and the epididymis. They occurred as variably sized, multifocal to coalescing, exophytic nodular, papillary and expansive masses on the surface of the testes and epididymis. The highest dose applied in males did not lead to systemic adverse effects and thus might be too low to detect any impact.

Increase in testes weight was evident in several studies and epididymis weight increase in one study. In these studies liver is a target organ of toxicity and the increase in testes weight was observed only at higher concentrations than liver weight increase. However, so far, there is no evidence that these effects are interlinked. Some evidence that BCPS might have an impact on testes also comes from the carcinogenicity study in rats.

Malignant mesothelioma originated from tissues covering the testes and the epididymides was observed in treated animals. Also, changes in uterus and ovary weights were observed in mice.

Thyroid pathway

In the master thesis of Åse-Karen Mortensen (2015) a strong binding affinity of BCPS to glaucous gull thyroid hormone transport protein transthyretin (TTR) is predicted.

According to the OECD thyroid scoping document (OECD, 2014) displacement of thyroid hormone from binding sites on TTR or thyroxin-binding globulin (TBG) represents a plausible biological process related to interference with the HPT axis that has been documented for a number of chemicals.

Summary

A concern for endocrine disruption is identified for BCPS for human health as well as for the environment. Nevertheless, a testing proposal Decision, requesting provision of an EOGRTS by 06 August 2021, was notified to the Registrant(s).. This study will provide further insight regarding the potential endocrine disrupting properties for BCPS.

Nevertheless, it is concluded that for BCPS a concern is also identified for possible endocrine disrupting properties for aquatic vertebrates: This concern is not followed up at the moment, as the identification of BCPS as a vPvB substance according to Art. 57e) of REACH is proposed.

Moreover, the concern for developmental neurotoxicity based on neurotoxic effects of structural analogues like polychlorinated biphenyls and the indications for an endocrine mode of action relevant for brain development is currently not followed up as the results from EOGRTS are awaited and as the identification of BCPS as a vPvB substance according to Art. 57e) of REACH is proposed.

7.11. PBT and vPvB assessment

Persistence

A full assessment of the environmental fate of BCPS is provided in section 7.7 above.

BCPS is not readily biodegradable and fulfils the criteria for "very persistent" in the sediment based on the OECD TG 308 study. BCPS is persistent (P) and very persistent (vP) in the sediment.

Bioaccumulation

A full assessment of the bioaccumulation potential of BCPS is provided in section 7.7 above.

Relevant outcomes are briefly summarised below:

- Screening criteria for aquatic bioaccumulation based on log K_{ow} is not fulfilled based on measured and predicted values.
- Calculated BCF values < 2000 (US EPA EPI Suite (ver. 4.1), BCFBAF v3.01 indicate a low potential for aquatic bioaccumulation. The measured lipid normalized BCF is 205, the study revealed some limitations (NITE, 2001).
- Field BMF values (fish, bird) are > 1.
- Field BMF values (herring, seals) are > 1.
- Highest BCPS levels constant over 30 years detected in fish-eating bird eggs (high trophic level).
- High BCPS levels detected in seals.
- Constant levels of BCPS detected in fish (perch, herring) over at least 10 years.
- Increasing BCPS trend in fish and birds.

- Screening criteria for terrestrial bioaccumulation are fulfilled.
- BCPS exhibits a very long half-life in rats and has a high affinity to adipose tissue.
- BCPS detected in human liver.

Using a weight of evidence assessment of the data available, BCPS meets the vB criteria in Annex XIII of REACH.

Toxicity

A full assessment of the environmental and human health hazard of BCPS is provided within sections 7.8 and 7.9 above. Relevant outcomes are briefly summarised below:

- For fish an OECD 203 limit study shows no toxicity at 0.98 mg/L.
- No chronic fish toxicity data are available, although there are indications for endocrine disruption.
- A 21d NOEC of 0.32 mg/L (reproduction) was identified in an OECD 211 study with Daphnia magna.
- In an OECD 201 study the 72h EC50 for growth rate and biomass was > 0.8 mg/L, the 72h NOEC for growth rate and biomass was 0.28 mg/L.
- Based on available in silico, in vitro and in vivo data it is concluded that BCPS has the potential for endocrine disrupting properties for aquatic vertebrates: This concern is not followed up at the moment, as the identification of BCPS as a vPvB substance according to Art. 57e) of REACH is envisaged to be considered in the proposed RMOA.
- The eMSCA supports the Registrants conclusion that BCPS is eye irritative and a classification according to Regulation 1272/2008/EC for Eye Irrit. Cat. 2 is warranted. No harmonised classification is proposed at the moment.
- Repeated dose toxicity studies demonstrate that liver is a target organ of BCPS toxicity, characterised by centrilobular hepatocyte hypertrophy, bile ducte hyperplasia and centrilobular degeneration. At higher doses increased kidney weight, increased incidence of nephropathy and decreased thymus weight were evident. Classification as STOT RE is not warranted as the observed effects are considered not severe enough at relevant doses.
- There is insufficient evidence to support a classification of the substance for mutagenicity and long term carcinogenicity studies do not demonstrate any carcinogenic properties.
- It is concluded that there are concerns for reproductive toxitixity, developmental immuno- and neurotoxicity as well as for endocrine disruption for human health. Nevertheless, as an EOGRTS is requested in dossier evaluation and should be available by 6. August 2021, more information relevant for these concerns will be presumably available.

Based on the currently available data, no conclusion on the T-criterion is currently possible.

7.12. Exposure assessment

Environmental exposure assessment

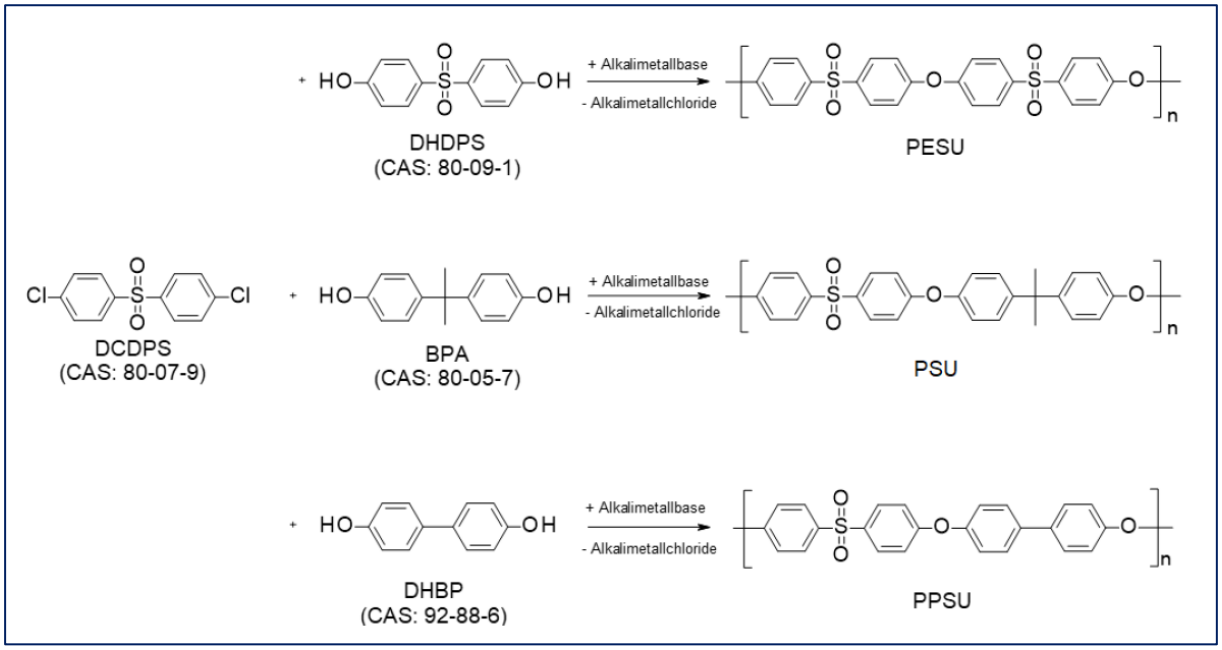
To the knowledge of the registrants, BCPS (abbreviated also as DCDPS) is used only as monomer in the industrial production of polyarylethersulfone polymers (PAES). The most common ones are polysulfone (PSU), polyethersulfone (PESU) and polyphenylenesulfone (PPSU).

Table 25 Identity of PAES-polymeres: PSU, PESU, PPSU

Code	Name	CAS	CAS-name
PSU	Polysulfone	25154-01-2	Phenol, 4,4'-(1-methylethylidene)bis-, polymer with 1,1'-sulfonylbis[4-chlorobenzene]

		25135-51-7	Poly(oxy-1,4-phenylensulfonyl-1,4-phenylenoxy-1,4-phenylenisopropyliden-1,4-phenylen)
PESU	Polyether-sulfone	25608-63-3	Phenol, 4,4'-sulfonylbis-, polymer with 1,1'-sulfonylbis[4-chlorobenzene]
		25667-42-9	Poly(oxy-1,4-phenylenesulfonyl-1,4-phenylene)
PPSU	Polyphenyl enesulfone	25608-64-4	[1,1'Biphenyl-4,4'-diol, polymer with 1,1'-sulfonylbis[4-chlorobenzene]

Table 26 Reaction schemes



Referring to ECHA's homepage, BCPS is manufactured and/or imported in the European Economic Area in 10.000 – 100.000 tonnes per year. It needs to be taken into account, that this range covers the substance as such but also already polymerized substance used for the manufacture of imported polymers. These polymers contain only residual amounts of BCSPS initially present (max. 100 ppm – given by the registrants), but the full amounts of monomere initially used are considered in the given tonnage range of 10.000 to 100.000 tonnes per year.

The global demand of PAES is around 53.000 tonnes per year. The demand in Europe is about 15.900 tons per year and split over many sectors. (Industry Experts – Aug 2016-publically available). Considering the monomer stoichiometry of PSU, PSU, PPSU, and the molecular weights of the monomers used, the demand for BCPS for the manufacture of these polymers is about the half of the polymere tonnage resulting in a European BCPS demand of roughly 8.000 tons per year (15.900/2).

Table 27 Tonnages of polymers in end-use sectors

Demand (annual)	Global volumes (tons)	European volumes (tons)	Volume (% total)
Aerospace	1.000	300	2%
Automotive	6.000	1.800	11%
Building & Construction	6.500	1.950	12%
Electronic & Electronics	4.000	1.200	8%
Food & Household	7.000	2.100	13%
Mechanical/Industrial	2.000	6.00	4%
Medical & Healthcare	17.000	5.100	32%
(others)	9.500	2.850	18%
Total/sum	53.000	15.900	100%

Environmental exposure

Referring to the life cyle of BCPS and PAES-polymers containing residual amounts of BCPS, the following stages are distinguished for environmental exposure.

(1)Industrial use of the substance as such

a) Manufacture of substance (source: registration dossier)

This chapter is confidential and not presented in the public version of this report.

b) Production of polymers (source: estimate of Registrant)

This chapter is confidential and not presented in the public version of this report.

(2)Use of polymers and articles containing residual amounts of substance

The polymers manufactured are used industrially for the manufacture of many articles. The articles are used by industrial workers, professionals and consumers. The polymers contain up to 100 ppm residual BCPS. The Registrant(s) expect the average residual content of BCPS to be lower than 100 ppm in polyarylethersulfone. Nevertheless, they could not confirm lower levels for their individual registrations or a representative value lower than 100 ppm covering all registrations. Regarding the duration of service life, the Registrant(s) estimate release to the environment to be low based on measurements of the polymers, experience so far and available public studies.

Considering potential food contact applications of their polymers (even if it is used differently), the PAES producers need to test the migration of substances with a specific migration limit (SML) according to EU regulation 10/2011/EC. PAES is checked for the migration of BCPSunder various (food contact) use conditions at several temperatures and using various 'food contact simulants'.

In addition, for ensuring the suitability of a specific consumer product for food contact applications (like kitchenware or kitchen machines), the company which puts this product on the market is responsible. This includes ensuring compliance to EU regulation 10/2011/EC regarding specific migration limits (SML).

Table 28 Examples of PAES-uses

Aerospace	Aircraft interior parts, airline catering trolleys and aircraft bezels, insultation foam
Automotive	Under the hood applications: battery caps, oils pumps, oil control pistons, ransmission parts, carburetor parts, bearing cages and ignition components, automotive fuses, car headlights, fuel systems

Building & construction	Faucet components, hot water fittings and plumbing manifolds (not the pipes)
Electronic & Electronics	Coil formers, plug-and-socket connectors, injection-molded printed circuit boards, parts for power circuit breakers, parts for power contactors and relays, transparent covers for signal lamps and switchboards, lamp holders and lampshades, heatshields, sensors, chip carriers, chip trays, battery seals, TV components, hairdryer parts, and oven, fan heater and projector components
Food & household	Beverage and food dispensers, micro wave dishes, meal/food service trays and as adhesive in cookware
Mechanical/Industrial	Manufacture of pumps and valves, oil level indicators, parts for pumps, parts for automatic beverage dispensers, parts for milking machines, parts for heat exchangers, packing for absorption and distillation columns, seals and conveyor belt idlers
Medical & Healthcare	Surgical trays, nebulizers and humidifiers and also in hemodialysis membranes, dialyzers, instruments, parts for instruments, surgical theater luminaries, sterilizing boxes, infusion equipment, secretion bottels and reuseable syringes, medical trays, surgical instrumental handles, dental instruments, ophthalmologic scopes, endoscopic devices, laboratory animal cages, medical tubing and anesthesiology equipment. Used in membrane applications such as gas separation membranes and membranes for drinking water filtration, bioprocessing and food and beverage processing
(others)	Membrane applications include particle filtration (waster water treatment), micro-filtration (clarification of beverages such as wine), ultra-filtration (bacteriological and virological decontamination of drinking water) and pretreatment for reverse osmosis (seawater desalination), powders are also used in paint and coating compounds

(3) Disposal of polymers and articles

Removal of BCPSin waste incineration plants

In case articles made of PAES are disposed in waste incineration plants, it needs to be checked if residues of BCPS in plastics during incineration are destroyed via high temperature. In order to elucidate upon applied temperatures in incineration plants, it is crucial to know which types of incineration plants are relevant for plastics waste.
- Municipal waste incineration plants
- Hazardous waste incineration plants
- Refuse derived fuel incineration plants

In corresponding plants waste has to be incinerated according to the obligations of Directive 2010/75/EC on industrial emissions according to which, as a minimum requirement "Waste incineration plants shall be designed, equipped, built and operated in such a way that the gas resulting from the incineration of waste is raised, after the last injection of combustion air, in a controlled and homogeneous fashion and even under the most unfavourable conditions, to a temperature of at least 850 °C for at least two seconds. Waste co-incineration plants shall be designed, equipped, built and operated in such a way that the gas resulting from the co-incineration of waste is raised in a controlled and homogeneous fashion and even under the most unfavourable conditions, to a temperature of at least 850 °C for at least two seconds." For further details, see Article 50 of Directive 2010/75/EC, also called IED directive (Directive 2010/75/EU, 2010).

BCPS is thermally stable up to 397 °C, where decomposition starts. Thus, the conditions in the waste incineration plant, e.g. at least 850 °C for two seconds, are sufficient to reliably incinerate the substance.

Disposal via landfills

The following estimate is based on calculations provided by the Registrant(s): The company 'Ramboll Deutschland GmbH' assessed the percentage of PESU plastic waste which is expected to be landfilled in Europe in various end-use sectors / industries. The Registrant(s) expect the percentage to be applicable for PAES as well. For an estimation of the PAES quantity to be landfilled, the EU demand – 15.900 tons/year- was used as the basis to estimate the waste quantities (= demand of PAES in Europe equals the waste volume of PAES in Europe) and related to the proportion to be landfilled. For the range 5% - 30%, 20 % was used in the quantity estimation, for '<5%', 5% was used.

Table 29 Tonnages of polymers in end-use sectors (assumption: EU demand = EU waste)

Use category	PAES Waste Quantity (tons)	% to landfill	Volume (% total)
Aerospace	300	5% - 30% (20%)	
Automotive	1.800	<5%	90
Building & Construction	1.950	5% - 30% (20%)	390
Electronic & Electronics	1.200	<5%	60
Food & Household	2.100	5% - 30% (20%)	420
Mechanical/Industrial	6.00	5% - 30% (20%)	120
Medical & Healthcare	5.100	5% - 30% (20%)	255
(others)	2.850	<5%	570
Total/sum	15.900		1965

Considering the treatment of polymer wastes in the individual end-use sectors and the total of 1.59 tons BCPS present in PAES (assumption 100ppm of 15.900 ton PAES), the amount of BCPS to be incinerated (and destroyed) is ~ 1.4 tons/year BCPS and the landfilled amount to be 0.2 tons/year in Europe.

Decomposition of PAES polymers are not expected to result in BCPSformation, as under environmental conditions during waste stage of PAES, free/active chlorine would be required to chlorinate the phenyl groups. Polymer aging breaks the chains at random locations, as there are no preferred breakage locations in these structures, but momers inside the bulk material could be released more easily after aging.

The Registrant(s) expect the average residual content of BCPS to be lower than 100 ppm in polyarylethersulfone. Nevertheless, they could not confirm lower levels for their individual registrations or a representative value covering all registrations.

Future perspectives

Waste volumes for landfill
The PAES market and thus the PAES volumes are growing in the "low single digit" - percentage range per year. Growing PAES usage might results in higher landfill waste volumes, however, the opposite trend in the EU towards environmental plastics litter reduction (microplastics / marine littering) will significantly reduce the amount of PAES waste to be landfilled. Incineration is the predominant waste disposal method.

Polymer Recycling

Production related PAES waste is almost fully recycled. In contrast, PAES post-consumer waste is practically not recycled, as the absolute volumes of PAES waste, as well as the relative volumes (% PAES in plastics waste) are far too low to establish a technically and

economically feasible PAES recycling system. Chemical recycling of PAES might be feasible in the future.

Human exposure assessment

BCPS is solid (m.p.: 147-150°C, b.p.: 397°C), has a low vapour pressure ($5.1x10^{-6}$ Pa) and slight water solubility (0.86 mg/L) at room temperature.

The substance is manufactured industrially as granular powder. Use of RMM and PPE are indicated in the registration data. Nevertheless, exposure of workers to the powder and the substance as such is possible during the manufacturing and following transfer processes. Potential inhalation and dermal exposure cannot be excluded fully. The registered particle size distribution of the powder is D_{10}=115 µm, D_{50}=240 µm, D_{90}=561 µm. The manufactured pellets are not considered to be dusty by the Registrant(s).

Regarding the manufacturing process of polymers, the range of different, potential activities is broader than the range of tasks for the manufacturing process of the substance itself. As they are performed at industrial sites, common and required RMM and PPE are expected to be applied. The risk potential of several tasks might be even significantly lower than uses covering the handling of the substance as manufactured, as the substance might have been already polymerized/consumed to high extents and kept in the matrix. Contact with the substance as such is only possible before the polymerization step.
Nevertheless, residual amounts of substance remain in the polymers. The degree and likeliness of migration and release leading to human exposure is expected to be low in this context.

7.13. Risk characterisation

No estimates are reported in this document.

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7.15. Abbreviations

BCF	bioconcentration factor
BMF	biomagnification factor
CAS	Chemical abstract service
ECHA	European Chemicals Agency
EOGRTS	Extended One Generation Toxicity Study
GEF	global evaluation factor
GLP	good laboratory praxis
M	mobility
MF	mutation frequency
MTD	maximal tolerable dose
NOAEL	no observed adverse effect level
PBT	persistent, bioaccumulative, toxic
RTG	relative total growth
WoE	Weight of evidence approach
vB	very bioaccumulative
vP	very persistent

7.16. Annex: Monitoring data in biota

BCPS levels in different organisms from 1971 until 2019 reported in literature, * median levels

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
Fish										
salmon (*Salmo salar*) 1 pool, n=10	-	muscle	low/ middle	8.7	**8.7**	LOD = 0.2 ng; LOQ = 3 * LOD	Gotland, Sweden	1971	Norström *et* al, 2004	
salmon (*Salmo salar*) 2 pool, n=4, total 8	-	muscle	low/ middle	31; 33	**32**	LOD = 0.2 ng; LOQ = 3 * LOD	Gotland, Sweden	1996	Norström *et* al., 2004 in K. Norström et al., 2010, in K. Norström PHD thesis 2006	↑
arctic char (*Salvelinus alpinus*) n=10	-	muscle		n.d	**n.d**	LOD = 0.47 ng/g l.w.	Fresh water lake (Vättern), Sweden	1972	Norström *et* al, 2004	
arctic char (*Salvelinus alpinus*) n=5	-	muscle		-	**1.8**	LOD = 1.1 ng/g l.w.	Fresh water lake (Vättern), Sweden	1996	Norström *et* al, 2004	↑
arctic char (*Salvelinus alpinus*) n=10	-	muscle		n.d.	**n.d.**	LOD = 0.2 ng; LOQ = 3 * LOD	Remote area, Lake, Abiskojaure, Sweden	1999	Norström *et* al, 2004	
perch (*Perca fluviatilis*) n=30	2-year old	muscle	low/ middle	40-100	-	n.i; recovery study and blank samples analysed	Latvia	1994	Olsson and Bergmann, 1995 in K. Norström *et* al., 2004 and K. Norström PHD Thesis, 2006	
perch n=10	2-year	muscle	low/ middle	70-88	**72**	n.i; recovery study and blank	Daugavgriva (influenced by	1994	Olsson and Bergmann, 1995	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
	old, 15-18cm, app. 45g					samples analysed	industrial discharge), Latvia			
perch n=10	2-year old 15-18cm, app. 45g	muscle	low/ middle	52-100	**76**	n.i; recovery study and blank samples analysed	Salacgriva (without local pollution), Latvia	1994	Olsson and Bergmann, 1995	
perch n=10	2-year old, 15-18cm, app. 45g	muscle	low/ middle	40-78	**56**	n.i; recovery study and blank samples analysed	Lielirbe (without local pollution), Latvia	1994	Olsson and Bergmann, 1995	
perch (*Perca fluviatilis*) n=62	2-year old	muscle	low/ middle	38 - 100	-	n.i; recovery study and blank samples analysed	Latvia	1994-95	Olsson et al 1999 i*n* K. Norström et al., 2004 and K. Norström PHD Thesis, 2006	
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	56-88	71	n.i., recovery analysed	Daugavgriva (influenced by industrial discharge), Latvia	1994	Olsson *et* al., 1999	
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	69-98	82	n.i., recovery analysed	Daugavgriva (influenced by industrial discharge), Latvia	1995	Olsson *et* al., 1999	
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	52-100	75	n.i., recovery analysed	Salacgriva (without local pollution)	1994	Olsson *et* al., 1999	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
							(=Kurmrags), Latvia			
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	38-71	61	n.i., recovery analysed	Salacgriva (without local pollution) (=Kurmrags), Latvia	1995	Olsson *et* al, 1999	
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	40-78	55	n.i., recovery analysed	Lielirbe (without local pollution), Latvia	1994	Olsson *et* al., 1999	
perch (*Perca fluviatilis*)	2-year old	muscle	low/ middle	46-72	53	n.i., recovery analysed	Lielirbe (without local pollution), Latvia	1995	Olsson *et* al., 1999	
perch (*Perca fluviatilis*) n=23	2-4 years old	muscle	low/ middle	28-190	**-**	n.i.	Latvia	1997	Valters *et* al., 1999 *in* K. Norström al., 2004 and and K. Norström PHD Thesis, 2006	
perch (*Perca fluviatilis*) n=2	one 2- or 3 years old, one 4 years old	muscle	low/ middle	48-57	**53**	n.i	Lielupe, Emburga, Latvia	1997	Valters *et* al., 1999	-
perch (*Perca fluviatilis*) n=4	three 2- or 3 years old, one 4 years old	muscle	low/ middle	74-120	**94**	n.i.	Kalnciems, Latvia	1997	Valters *et* al., 1999	
perch (*Perca fluviatilis*) n=4	one 2- or 3 years old	muscle	low/ middle	140-190	**160**	n.i.	Sloka, Latvia	1997	Valters *et* al., 1999	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
perch (*Perca fluviatilis*) n=5	one 2- or 3 years old	muscle	low/ middle	39-58	**48**	n.i.	Daugava, Lielvarde, Latvia	1997	Valters *et* al., 1999	
perch (*Perca fluviatilis*) n=5	one 2- or 3 years old	muscle	low/ middle	28-38	**32**	n.i.	Dole, Latvia	1997	Valters *et* al., 1999	
perch (*Perca fluviatilis*) n=3	one 2- or 3 years old	muscle	low/ middle	38-50	**44**	n.i.	Daugavgriva, Latvia	1997	Valters *et* al., 1999	
perch	-	muscle	low/ middle	38	**38**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Near river Daugava, Latvia	2008	K. Norström *et* al., 2010	
perch (*Perca fluviatilis*) n=5	-	muscle	low/ middle	-	**15**	LOD = 0.2 ng; LOQ = 3 * LOD	Northern baltic coast, Island Holmön, Sweden	1998	Norström *et* al., 2004	
perch (*Perca fluviatilis*) n=5	-	muscle	low/ middle	-	**16**	LOD = 0.2 ng; LOQ = 3 * LOD	Northern baltic coast, Island Holmön, Sweden	1998	Norström *et* al., 2004	
Perch (*Perca fluviatilis*) n=5	-	muscle	low/ middle	-	**35**	LOD = 0.2 ng; LOQ = 3 * LOD	Souther Baltic coast, Kvädöfijärden, Sweden	1998	Norström *et* al., 2004	
perch (*Perca fluviatilis*) n=5	-	muscle	low/ middle	-	**37**	LOD = 0.2 ng; LOQ = 3 * LOD	Souther Baltic coast, Kvädöfijärden, Sweden	1998	Norström *et* al., 2004	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
perch	-	muscle	low/ middle	-	**20**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Kvädöfjarden, Sweden	?	Norström *et* al., 2010	
perch	-	muscle	low/ middle	-	**36**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Holmön, Sweden	?	Norström *et* al., 2010	
perch	-	muscle	low/ middle	-	**42**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Western coast of Saaremaa Island, Estonia	2008	Norström *et* al., 2010	
perch	-	muscle	low/ middle	-	**69**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Coastal area near Sillamäe, Estonia	2008	Norström *et* al., 2010	
perch	-	muscle	low/ middle	-	**46**	LOD = 3 times the SD of blank sample noise. LOQ was used.	Szczecin, Lagoon, Poland	2008	Norström *et* al., 2010	
pelagic Baltic herring (Clupea haengus) n=10		muscle	low/ middle	-	29	LOD = 0.2 ng; LOQ = 3 * LOD	Baltic sea, Landsort, Sweden	1998	Norström et al., 2004 in K. Norström et al., 2010	
pelagic Baltic herring (*Clupea haengus*) n=10		muscle	low/ middle	-	31	LOD = 0.2 ng; LOQ = 3 * LOD	Baltic sea, Landsort, Sweden	1998	Norström et al., 2004 in K. Norström et al., 2010	
herring	-	-	low/ middle	-	33	LOD = 3 times the SD of blank sample noise. LOQ was used.	Kvädöfjärden, Sweden	-	Norström *et* al, 2010	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
herring	-	-	low/ middle	-	17	LOD = 3 times the SD of blank sample noise. LOQ was used.	Fladen, Sweden	-	Norström *et* al, 2010	
herring	-	-	low/ middle	-	58	LOD = 3 times the SD of blank sample noise. LOQ was used.	Utlängen, Sweden	2008	Norström *et.* al, 2010	
herring	-	-	low/ middle	-	32	LOD = 3 times the SD of blank sample noise. LOQ was used.	Gulf of Gdansk, Poland	2008	Norström *et*. al, 2010	
herring	-	-	low/ middle	-	26	LOD = 3 times the SD of blank sample noise. LOQ was used.	Coastal area north from Klaipeda, Lithuania	2008	Norström *et.* al, 2010	
bream n=4	-	muscle	low/ middle	3,4 - 34	-	n.i.	Germany, freshwater (Elbe, Rhein)	1997	in Norström PHD Thesis 2006 and in Norström *et* al., 2004 and in Norström *et.* al, 2010	
SEALS										
grey seal n=3		blubber	high	53 - 88	70.5	n.i.	Hudiksvall, Sweden	1993	Olsson, 1995 in Norström,2006 and in PHD thesis Norström 2006	
grey seal 1 pool, n=5	-	blubber	high	-	68	LOD = 0.2 ng; LOQ = 3 * LOD	Swedish East coast, Sweden	1995 - 97	Norström *et* al., 2004 and in PHD thesis Norström 2006	
grey seal n=1	7 yrs	blubber	high	49; 49	49	LOD = 0.2 ng; LOQ = 3 * LOD	Swedish East coast,	1996	Norström *et* al., 2004	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
							Öxelösund, Sweden			
grey seal n=1	6 yrs	blubber	high	73; 68	70.5	LOD = 0.2 ng; LOQ = 3 * LOD	Bothnian Bay, Sweden	1996	Norström *et* al., 2004	
(Grey seal, n=1 unhealthy individual)	11 yrs	blubber	high	470; 480	475	LOD = 0.2 ng; LOQ = 3 * LOD	Sthlm. Archipelago, Baltic coast, Sweden	1996	Norström *et* al., 2004	
grey seal n=1	10 yrs	blubber	high	98; 98	98	LOD = 0.2 ng; LOQ = 3 * LOD	Bothnian Sea, Sweden	1997	Norström *et* al., 2004	
grey seal n=10	6 – 16 yrs	blubber	high	41 - 240	60*; 140.5	LOQ for BCPS 3.5 ng, calculated as 5 times the mean background amount (0.7 ng) in the blank solvent sample	Northern Baltic sea, Bothanian Sea and Bay, Sweden	2000-01	Larsson *et* al., 2004, cited in Norström,2006 and in PHD thesis Norström 2006	
grey seal n=10	6 – 16 yrs	liver	high	55 - 700	200*, 377.5	LOQ for BCPS 3.5 ng, calculated as 5 times the mean background amount (0.7 ng) in the blank solvent sample	Northern Baltic sea, Bothanian Sea and Bay, Sweden	2000-01	Larsson *et* al., 2004 cited in K. Norstrom,2006 and in PHD thesis Norström 2006	
grey seal n=10	6 – 16 yrs	lung	high	21 - 98	29*, 59.5	LOQ for BCPS 3.5 ng, calculated as 5 times the mean background amount (0.7 ng)	Northern Baltic sea, Bothanian Sea and Bay, Sweden	2000 -2001	Larsson *et* al., 2004 in Norström, 2006 and in PHD thesis Norström 2006	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
						in the blank solvent sample				
BIRDS										
black skimmer (*Rynchops niger*) n=4	unknown	egg	high	identified in 3 individuals	-	peak identified	Salt works colony, California, USA	2011	Millow *et* al., 2015	Not possible
white-tailed sea eagle n=21	unknown	egg	high	n.d. - 16	-	n.i.	Baltic coast, Sweden	1971-76	Helander *et* al. 2002 in Norström et al., 2010	
white-tailed sea eagle n=21	unknown	egg	high	7.4 – 610	170 110	n.i.	Baltic coast, Sweden	1987 - 91	Helander *et* al. 2002, in PHD Thesis Norström 2006	
white-tailed sea eagle n=1	unknown	egg	high	500	-	n.i.	Söderköpnig, Sweden	1987	Olsson, 1995, in PHD Thesis Norström 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	1100 - 2600	1400*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1971	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	1100 - 1900	1500*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1976	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	High	810 – 1500	1200*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1981	Jörunddsdottir *et* al. 2006	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	900 – 1400	1100*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1986	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	780 – 1200	900*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1991	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	770 – 980	890*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	1996	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=5	unknown	replacement egg	high	760 - 1400	1000*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	2001	Jörunddsdottir *et* al. 2006	
guillemot (*Uria aalge*) n=10	unknown	egg	high	850-1300	1100*	Recovery 88% with amount of 0.06 µg, n=5	Stora Karlsö, island in the Baltic Sea, Sweden	2003	Values are from Jörunddsdottir et al. 2006 cited in Jörunddsdottir et al. 2008	
Guillemot (*Uria aalge*) n=5	unknown	Breast muscle	high	-	1900	LOD = 0.2 ng; LOQ = 3 * LOD	Stora Karlsö, island in the Baltic Sea, Sweden	1989	Norström *et* al., 2004 in Norström *et* al., 2010, in PHD Thesis K. Norström 2006	
guillemot (*Uria aalge*) n=5	unknown	Breast muscle	high	-	1600	LOD = 0.2 ng; LOQ = 3 * LOD	Stora Karlsö, island in the Baltic Sea, Sweden	1989	Norström *et* al., 2004 in Norström *et* al., 2010, in PHD Thesis K. Norström 2006	
guillemot (*Uria aalge*) *n*=10	unknown	egg	high	5.1 – 8.8	6.4	LOQ = 3.2 ng/g fat	Vestmanna-eyjar Iceland	2002	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
guillemot (*Uria aalge*) n=10	unknown	egg	high	4.5 - 16	6.7	LOQ = 3.2 ng/g fat	Sandøy, Faroe Islands	2003	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	
guillemot (*Uria aalge*) n=10	unknown	egg	high	3.3 - 10	6.2	LOQ = 3.2 ng/g fat	Bjørnøya, Norway	2005	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	
guillemot (*Uria aalge*) n=10	unknown	egg	high	6.3 - 17	10	LOQ = 3.2 ng/g fat	Hjelmsøya, Norway	2005	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	
guillemot (*Uria aalge*) n=10	unknown	egg	high	n.d - 18	10	LOQ = 3.2 ng/g fat	Sklinna, Norway	2005	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	
guillemot (*Uria aalge*) n=10	unknown	egg	high	850-1300	1100	LOQ = 3.2 ng/g fat	Stora Karlsö Sweden	2003	Jörunddsdottir *et* al. 2009 b Jörunddsdottir *et* al. 2008	
guillemot (*Uria aalge*)	unknown	egg	high	760 - 2600	1680	BCPS to 3.2 ng/g fat	Sweden	1971 - 2001	Jörunddsdottir *et* al., 2009 b in K. Norström *et* al., 2010	
guillemot (*Uria aalge*)	unknown	egg	high	5.1 – 8.8	7	BCPS to 3.2 ng/g fat	Iceland	2002	Jörunddsdottir *et* al., 2009 b in K. Norström *et* al., 2010	
guillemot (*Uria aalge*)	unknown	egg	high	4.5 - 16	10.2	BCPS to 3.2 ng/g fat	Faroe Islands (remote)	2003	Jörunddsdottir *et* al., 2009 b in K. Norström *et* al., 2010	
guillemot (*Uria aalge*)	unknown	egg	high	n.d. - 18	18	BCPS to 3.2 ng/g fat	Norway / North Sea	2005	Jörunddsdottir *et* al., 2009 b in K. Norström *et* al., 2010	
hering gull (*Larus argentatus*) n=1	unknown	egg	high	identified	-	n.i.	Canada	1989	Letcher *et* al., 1995 cited in K. Norström *et* al., 2006	

Species/ No. ind. (n)	Age or gram /length	Tissue	Trophic level	BCPS ng/g l.w.	average values ng/g l.w.	LOD/LOQ	Location	Year	Reference	Trend
glaucous gull n=87		plasma	High	5.2 - 143	-	see below	Norway / North Sea	2002 - 04	Verreault *et* al., 2005 cited *in* K. Norström et al., 2010 and PHD thesis Norström 2006	
glaucous gull (male), n=42	unknown	blood (plasma)	high	8.15 – 143 ng/g wet weight	26.5 ± 10.8	LOD: 0.001 - 0.35 ng/g wet weight	Bear Island / Artic Norway	2002 - 2004	Verreault *et* al., 2005	not possible
glaucous gull (female) n=42	unknown	blood (plasma)	high	5.24 – 58.8 ng/g wet weight	19.5 ± 3.56	LOD: 0.001 - 0.35 ng/g wet weight	Bear Island / Artic Norway	2002 - 2004	Verreault *et* al., 2005	not possible
common Gull		eggs	high	ng/g w.w	0.20	n.i.	Urban area around Tromsø, Norway	2017	Screening programm 2017 (2018)	
Other organisms										
mink		liver		ng/g w.w	0.53	n.i.	Arctic	2017	Screening programm 2017 (2018)	
Humans										
human n=6		Liver	high	~2-40 ng/g lipid	-	n.i.	Germany	-	Ellerichmann *et* al., 1998 cited in K. Norström PHD Thesis 2006	

n.i. not idndicated; * geometric measn concentrations