SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

N,N'-dithiodi-o-phenylenedibenzamide

EC No 205-201-9

CAS No 135-57-9

Evaluating Member State(s): Belgium

Dated: 25 February 2020

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Before concluding the substance evaluation a Decision to request further information was issued on 8 March 2016.

Further information on registered substances here:

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

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

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

N,N'-dithiodi-o-phenylenedibenzamide (trade name DBD) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB

- Exposure of the environment

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

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	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

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

No need for follow-up actions.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X

In order to clarify the PBT/vPvB concern of the substance, an aerobic mineralisation study in surface water, according to OECD TG 309 was requested in a Substance Evaluation Decision dated 8 March 2016.

The parent compound DBD disappears rapidly from the water in the simulation study (DT_{50} = 1 d at 12 °C) and a significant number of degradation products is formed. Mineralisation however is negligible (<2 % CO_2 formation after 60 days).

Eighteen major degradation products are detected, quantified and tentatively identified. It can be concluded that the parent compound DBD is not persistent, but that some of its degradation products are stable and fulfill the P and/or vP criterion in fresh water. Full identification of the degradation products however could not be achieved. Thus, the identity of the formed degradation products remains hypothetical. Plausible chemical structures are suggested for several of the degradation products.

QSAR estimated BCFs for DBD, using the experimentally determined log K_{ow} of 4.0, do not indicate aquatic bioaccumulation potential for the parent compound, whereas some of the estimated BCF/BAF values using the estimated log K_{ow} value of 4.59 indicates that DBD is a bioaccumulative substance.
Further, the eMSCA considers that the degradation products (tentatively identified) are not bioaccumulative for aquatic organisms as the screening criterion is not met (estimated log K_{ow} <3). Some uncertainty remains however since the degradation products have only been tentatively identified.

It is therefore concluded that the parent compound DBD is not a PBT/vPvB substance and that it is unlikely that any of the relevant degradation products are PBT/vPvB.

5.2. Other actions

Not applicable.

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

Not applicable, see section 5.

Part B. SUBSTANCE EVALUATION

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

N,N'-dithiodi-o-phenylenedibenzamide (DBD) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB

- Exposure of the environment

Table 3

EVALUATED ENDPOINTS Endpoint evaluated	Outcome / conclusion
Potential PBT/vPvB	Concern not substantiated. No further action. The parent compound DBD is not persistent. Some of the degradation products are persistent, but they are unlikely to be bioaccumulative (screening criterion is not met). Some uncertainty remains since the identity of the formed degradation products remains hypothetical.
Exposure of the environment	Not evaluated since the PBT concern is not confirmed.

7.2. Procedure

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected PBT/vPvB and exposure of the environment, N,N'-dithiodi-o-phenylenedibenzamide was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of Belgium was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation, the Competent Authority of Belgium has initiated the substance evaluation for N,N'-dithiodi-o-phenylenedibenzamide, CAS No 135-57-9 (EC No 205-201-9) based on registration(s) submitted by the Registrant(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the suspected PBT/vPvB concern. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted a draft decision to ECHA on 18 March 2015.

A unanimous agreement of the Member State Committee on the draft decision was reached on 23 November 2015 in a written procedure. ECHA notified the registrant(s) of the decision pursuant to Article 51(6) of the REACH Regulation on 8 March 2016 requesting an aerobic mineralisation study in surface water (OECD 309 at 12 °C). Moreover it was requested that a soil simulation study was to be conducted if the aerobic mineralisation study in surface water wouldn't allow to conclude that N,N'-dithiodi-o-phenylenedibenzamide is persistent or very persistent according to Annex XIII of the REACH Regulation.

In accordance with Article 46(2) of REACH the registrant(s) updated their dossier on 28 November 2017 with the requested Aerobic mineralisation study in surface water.

In accordance with Article 46(3) of REACH, the evaluating Member State started the second round of the evaluation without undue delay.

In accordance with Article 46(4) of REACH, the evaluating Member State finished its evaluation activities within 12 months of the information being submitted.

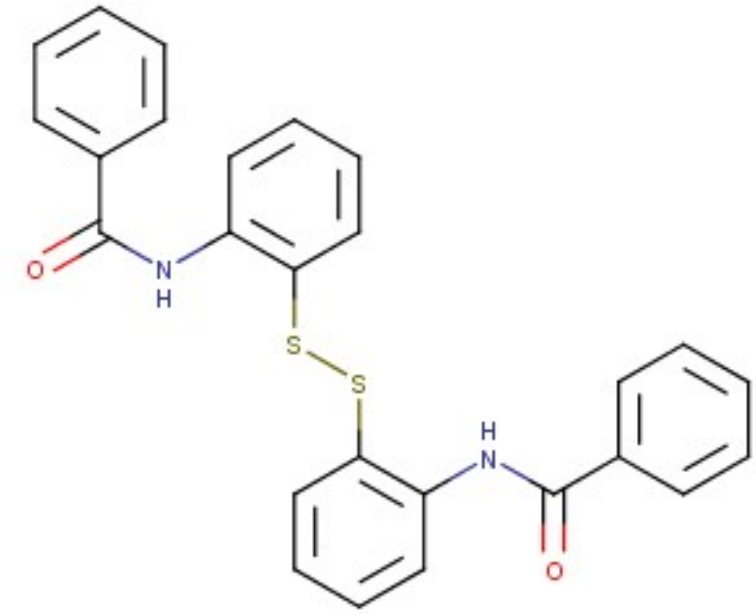
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	N,N'-dithiodi-o-phenylenedibenzamide
EC number:	205-201-9
CAS number:	135-57-9
Index number in Annex VI of the CLP Regulation:	Not listed
Molecular formula:	$C_{26}H_{20}N_2O_2S_2$
Molecular weight range:	456.58 g/mole
Synonyms:	DBD Pepton 22 N-{2-[(2-benzamidophenyl)disulfanyl]phenyl}benzamide

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

Structural formula:



7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Yellow powder with odour charceristic for sulfur-containing compounds (by observation)
Vapour pressure	3.85 E-13 Pa at 25 °C (Modified Grain method)
Melting Point	143 °C (Capillary Method)
Water solubility	0.048 mg/L at 20 °C and pH 6.4-6.7 (OECD TG 105-column elution method)
Partition coefficient n-octanol/water (log K_{ow})	Log K_{ow} = 4.0 (EU A.8-HPLC method)
Flammability	MIE (mimimum ignition energy) 34 mJ (non-guideline)
Explosive properties	Non explosive (According to BS6713, ISO6184 Part 1 (1985))
Granulometry	<300 µm: 68.8 % <150 µm: 63.2 % <106 µm: 26.8 % <90 µm: 17.6 %

	<75 µm: 10.2 % <63 µm: 1.6 % <53 µm: 0.8 % Median particle size between 106 and 150 µm. Less than 1 % respirable fraction (<10 µm) (According to BS410)

7.5. Manufacture and uses

7.5.1. Quantities

Table 7 (dissemination website consulted on 20 September 2018)

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

Table 8 (dissemination website consulted on 20 September 2018)

USES	Use(s)
Uses as intermediate	/
Formulation	Formulation and repacking of substance Formulation and (re)packing of substances and mixtures
Uses at industrial sites	Production of tyres and rubber goods Storage, metering and mixing of substance (or mixture) with other substances/mixtures in rubber article and polymer manufacture
Uses by professional workers	/
Consumer Uses	/
Article service life	By professionals: tyre mounting and dismounting and handeling of technical rubber goods, retreading Storage, metering and mixing of the substance (or mixture) with other substances/mixtures in rubber article and polymer manufactur (by workers) By consumers: use of rubber goods (vehicles, electrical batteries and accumulators, rubber articles, plastic articles), use of tyres

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Not listed in annex VI.

7.6.2. Self-classification

- In the registration(s):

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

  Aquatic chronic 4, H413: May cause long lasting harmful effects to aquatic life

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (Classification available in C&L inventory on 20 September 2018):

  Eye irrit. 2, H319: Causes serious eye irritation

  Aquatic Acute 1, H400: Very toxic to aquatic life

  Aquatic Chronic 1, H410: Very toxic to aquatic life with long lasting effects

  Aquatic Chronic 3, H412: Harmful to aquatic life with long lasting effects.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

Due to the low water solubility of the substance (0.048 mg/L) a hydrolysis study was not performed.

In the simulation study in surface water according to OECD guideline 309 (see paragraph 7.7.1.2.2.), a half-life of ca. 1 day for the parent compound is determined. A chemical analysis of the sterile control vessels is not performed, so it is not possible to decide whether the observed degradation of DBD is a biotic or abiotic process.

7.7.1.1.2. Phototransformation in air

Using the QSAR program AOP v1.92 from EpiSuite an overall hydroxyl radicals reaction rate constant of 2.44 x 10^{-10} cm^3/molecule.sec is calculated resulting in an estimated half-life in air of 0.562 hours.

7.7.1.2. Biotic degradation

7.7.1.2.1. Biodegradation in water : screening tests

Table 9 : Screening tests for biodegradation in water

Method	Results	Remarks	Reference
Ready biodegradability OECD TG 301B (CO_2 evolution test)	% degradation (CO_2 evolution): 9.5 after 28 d 9.9 after 35 d 10.3 after 42 d 10.5 after 49 d 8.6 after 56 d	Reliability 1 GLP Key study Inoculum = aerobic activated sludge	Registration dossier, (2014c) study report
Ready biodegradability EU C.4-E (closed bottle test) equivalent or similar to OECD Guideline 301 D (closed bottle test)	% degradation (O_2 consumption): 14 after 7 d 6 after 14 d 5 after 21 d 17 after 28 d 27 after 42 d 20 after 49 d 22 after 56 d 17 after 60 d	Reliability 1 GLP Key study Deviations: duration of test extended up to 60 days Purity: 96.5%	Registration dossier, (2014a) study report
Qualitative and quantitative analysis of the ready biodegradability study EU C.4-E (closed bottle test)	27% degradation after 42 days. Identification of 2 metabolites (no quantification): N-(2-[(2-aminophenyl)disulfanyl]phenyl)benzamide formed by oxygen consumption and N-[(1E)-4-oxo-2-sulfanylcyclohexa-2,5-dien-1-ylidene]benzamide formed by cleavage of the parent substance	Reliability 2 Non GLP Supporting study Starting concentration: 500 µg/L (10 fold above the water solubility)	Registration dossier, (2014a) study report
Ready biodegradability OECD TG 301B (CO_2 evolution) EU Method C.4-C (CO_2 evolution)	% degradation (CO_2 evolution): 24 after 28 d	Reliability 1 GLP supporting study Purity: 95.97%	Registration dossier, (1995a) study report
Ready biodegradability equivalent or similar to OECD TG 301 C (Modified MITI Test (I))	% degradation (O_2 consumption): 0 after 28 d	Reliability 2 Non GLP supporting study	Registration dossier, (1989a) study report

No biodegradation of DBD was seen in a ready biodegradability test (OECD TG 301C (modified MITI test (I)) after 28 days.

In two other ready biodegradability tests (OECD TG 301B: CO_2 evolution test) respectively 24% and 9.5% degradation were observed after 28 days.

Another study (EU C.4-E: closed bottle test) confirmed the low biodegradation potential of the substance: 5% after 21 days and 17% after 60 days.

In a supplementary study to EU C.4-E, an analysis was made to identify the metabolites. After 42 days, the parent compound (intial concentration: 500 µg/L which is more than 10 fold above the water solubility) was degraded for 27%. The parent compound was quantified in concentrations of 21 µg/L, 0.8 µg/L and 3.4 µg/L after 0, 35 and 42 days respectively, which indicates that the low water solubility and high adsorption potential to biomass or glass walls may explain the low biodegradation potential (stops at around 27%).

Two metabolites could be identified after 42 days and possible structures were defined, but could not be quantified:
- N-{2-[(2-aminophenyl)disulfanyl]phenyl}benzamide formed by biotic or abiotic cleavage of one amide function and release of benzoic acid. The formation of benzoic acid could explain the oxygen consumption during the test.
- N-[(1E)-4-oxo-2-sulfanylcyclohexa-2,5-dien-1-ylidene]benzamide formed by cleavage of the disulfide bond with subsequent hydroxylation and oxidation.

Therefore, the eMSCA concludes that DBD is not readily biodegradable.

7.7.1.2.2. Biodegradation in water and sediment : simulation tests

Table 10 : Simulation test in water and sediment

Method	Results	Remarks	Reference
Biodegradation in surface water OECD TG 309 (Aerobic Mineralisation in Surface Water), including a kinetic and degradation pathway study	Half-life of parent compound DBD: <1 d (at 12 °C) % mineralisation (CO_2 evolution): <2 after 60 days 18 “major” transformation products could be detected of which 4 are considered to be key metabolites: MP1: DT_{50} = 514 d * MP2: DT_{50} = 312 d * MP3: DT_{50} = 32 d MP4: DT_{50} = 55 d	Reliability 1 GLP Radiochemical purity: 97.1% Duration of the test: 60 days	 Registration dossier, (2017a) study report

* There remains some uncertainty on the reliability of these half-life values as some of them exceed by far the study period and the statistical validity is poor.

On request of ECHA (substance evaluation decision of 8 March 2016), an aerobic simulation study in freshwater according to OECD TG 309 was conducted to clarify the suspected

PBT/vPvB concern of DBD. More clarification was needed on the extent that the substance degrades, which metabolites are formed and in which quantity.

The study was performed at 12 °C with surface water from Calwich Abbey lake (Staffordshire, England) which was treated with radiolabelled test item (initial concentrations of 1 µg/L and 24 µg/L).

Eighteen major degradation products (i.e. defined as present in more than 1 % at two or more consecutive time points or present above 5 % at any individual time point) were detected in the chromatographic analysis. Potentially there are even more than 18 degradation products. The assessment of metabolite kinetics was focused on four key degradation products (MP1, MP2, MP3 and MP4) that were detected at time points 0 and 0.2 DAT and remained detectable until the termination of the incubation phase at 60 DAT. The kinetic modelling software KinGUII version 2.1 was used to estimate the degradation kinetics. Degradation half-lives were predicted using the single first order (SFO) kinetic model.

The parent substance DBD disappeared rapidly from the surface water (DT_{50} = 1 day at 12 °C) and a significant amount of degradation products were formed. Mineralisation measured as CO_2-formation however was negligible (<2% after 60 days).

Table 11: Kinetic summary of the degradation of DBD and key metabolites.

Component	Model	DT_{50} (days)	DT_{90} (days)	Chi^2 error (%)	t-test
DBD	SFO	1	3.38	13.07	<2e-16
MP1	SFO	514	>1000	30.02	0.3733
MP2	SFO	312	>1000	18.82	0.1815
MP3	SFO	32	107	22.03	0.0002
MP4	SFO	55	184	14.94	2.16e-06

It should be noted that in the ECHA Guidance on Information Requirements and Chemical Safety assessment (Chapter R.11, PBT/vPvB Assessment v.3.0) it is stated that "*in general transformation products detected at ≥ 10% of the applied radioactivity in the total water-sediment system at any sampling time should be identified unless reasonably justified otherwise. Transformation products for which concentrations are continuously increasing during the study should also be considered for identification, even if their concentrations do not exceed the limits given above, as this may indicate persistence. The latter should be considered on a case by case basis."* For three additional degradation products, M7, M8 and M10a, the maximum concentrations are respectively 10.34% at DAT 60, 13.02% at DAT 29 and 12.19% at DAT 15. For metabolite M10a, the P criterion is fulfilled, while this is unknown for metabolite 7 (as the timepoint of max occurrence was 60 days) and for metabolite 8 no reliable value could be determined due to scatter, poor model fit and/or no apparent pattern in data points.

A more detailed assessment is provided in the confidential annex (not available in published version).

Based on the results presented in this simulation study in surface water, the eMSCA concludes that the parent compound DBD readily undergoes primary degradation in surface water and that DBD forms a high number of degradation products. It is therefore concluded that the parent compound DBD is not persistent in surface water, but some of the formed metabolites are persistent or even very persistent in surface water.

Moreover, in a follow-up study (2017b) an attempt was made to determine the chemical structure of the degradation products detected in the aerobic mineralisation study using liquid chromatography high resolution mass spectrometry (LC-HRMS). At least 18 major degradation products (primary, secondary or tertiary) could be detected. For some of these

degradation products, the chemical identity is suggested and an overall transformation pathway has been proposed. Comparing the results from the HPLC-βRAM analysis with those from the HPLC-MS analysis shows that MP2, MP3 and MP4 respectively potentialy correspond to the following compounds: bis-hydroxylated N-BATP (estimated log K_{ow} = -1.0), tris-hydroxylated N-BATP (estimated log K_{ow} = -1.0) and N-[2-(methylthio)phenyl]benzamide (estimated log K_{ow} = 2.7). Unfortunately, full proof of the chemical identity cannot be provided because a certified analytical reference standard is not available. A full proof identification should also rely on a second chromatographic method that is distinctly different from the first one, i.e. variation in mode of separation, solid phase and elution solvents. Examining the degradation pattern in such detail was in practice not possible.

As explained under section 7.7.3, a qualitative assessment of the degradation products indicates that they are unlikely to fulfil the criterion for bioaccumulation. Therefore, in the framework of the PBT assessment, the eMSCA doesn't consider the lack of a more detailed degradation pattern/identification of the degradation products as problematic.

7.7.1.2.3. Biodegradation in soil : simulation tests

A simulation test in soil is not available for DBD. In the Substance Evaluation Decision (dated 8 March 2016) on DBD a simulation test in soil was requested if the results from the simulation test in surface water would not allow to conclude that DBD is persistent or very persistent according to Annex XIII of REACH.

The eMSCA carefully examined the results of the simulation study in surface water. The parent compound degrades very rapidly in water and is not persistent, but several degradation products meet the (v)P-criterion. Therefore, the eMSCA concludes that in this case further biodegradation testing in soil is unnecessary.

Indeed, the half-life of 1 day in surface water of the parent compound DBD is far below the persistence threshold value (i.e. 40 days). Therefore, it is unlikely that the parent compound DBD would meet the persistence criterion in soil. Moreover, it is unlikely that the degradation pattern of DBD in soil will differ substantially from the degradation pattern in water.

7.7.2. Environmental distribution

7.7.2.1. Adsorption / desorption

Table 12 : Studies on adsorption / desorption

Method	Results	Reference
K_{oc} estimation using EpiSuite v4.10 (KOCWIN v2.00)	K_{oc} = 34 000 L/kg (MCI method), log K_{oc}: 4.532 K_{oc} = 432.4 L/kg (Kow method), log K_{oc}: 2.636	Registration dossier, (2014d) EpiSuite v4.10

The eMSCA concludes that DBD has a strong potential to bind to soil and thus has the tendency to dissipate from surface water to soil and sediment.

7.7.2.2. **Distribution modelling**

The eMSCA examined the expected distribution of DBD with the Mackay environmental fugacity model III (EpiSuite v4.1). The following values were introduced in this estimation model: water solubility = 0.048 mg/L; log K_{ow} = 4.

	Amount (%)	half-life (hr)	emissions (kg/hr)
Air	0.02	1.05	1000
Water	9.25	1440	1000
Soil	67	2880	1000
Sediment	23.7	13000	0

The model predicts that the substance distributes to water (9 %), sediment (24 %) and soil (67 %) if equal emission to air, water and soil is assumed.

7.7.3. Bioaccumulation

7.7.3.1. **Aquatic bioaccumulation**

Table 13 : Aquatic bioaccumulation studies on DBD

Method	Results	Remarks	Reference
EU A.8 (partition coefficient) HPLC method	K_{ow}=1.0 x 10^4 Log K_{ow} = 4.0	Reliability 1 GLP Purity: 95.97 %	Registration dossier, (1996a) study report
Bioaccumulation Estimates BCFBAF v3.00 with a log K_{ow} of 4.0	Log BCF from regression-based method = 0.97 (BCF = 9.24 L/kg wet-wt) Log Biotransformation Half-life (HL) = 0.1616 days (normalised to 10 g fish) Including biotransformation: Log BCF Arnot-Gobas method (upper trophic) = 1.81 (BCF = 65 L/kg wet-wt) Log BAF Arnot-Gobas method (upper trophic) = 1.81 (BAF = 65 L/kg wet-wt) Excluding biotranformation:	Reliability 2*	Registration dossier, (2014e) EpiSuite v4.10

Method	Results	Remarks	Reference
	Log BCF Arnot-Gobas method (upper trophic) = 3.01 (BCF = 1034 L/kg wet-wt) Log BAF Arnot-Gobas method (upper trophic) = 3.37 (BAF =2360 L/kg wet-wt)		
CAESAR QSAR model	BCF = 25 L/kg	Reliability 2*	Registration dossier, (2011) CAESAR QSAR

*reliability 2 : in the registration dossier the study is given reliability 1, however eMSCA considers it to be reliability 2 as this is a QSAR estimate.

KOWWIN v1.68 estimates a log K_{ow} of 4.59, while the experimentally determined log K_{ow} for DBD is 4.0, which is close to the cut off B-screening criterion of 4.5.

QSAR estimates predict a BCF of 25 L/kgwwt (CAESAR) and 9.24 L/kgwwt (BCFBAF v3.01), which indicates that DBD has no potential to bioaccumulate in aquatic organisms. According to the Arnot-Gobas estimates the BCF and BAF range between 65 L/kgwwt (BCF upper trophic) and 90.1 L/kgwwt (BAF lower trophic) when biotransformation is taken into account. Without biotransformation the Arnot-Gobas method estimates a BCF of 1034 L/kgwwt and a BAF of 2360 L/kgwwt.

The 4 key metabolites detected in the simulation study in freshwater (see 7.7.1.2.2.) are all eluted in the HPLC analysis before the parent compound DBD. The experimentally determined retention times are:

DBD: 18.40 minutes

MP4: 15.50 minutes

MP3: 13.40 minutes

MP2: 12.10 minutes

MP1: 7.30 minutes

Even though the identity of these degradation products is not known with certainty, they are probably not bioaccumulative as they are more hydrophilic than DBD. Therefore, the log K_{ow}-values of the degradation products will be lower than 4.0 (= experimentally measured value for DBD) and consequently they all screen as not bioaccumulative for aquatic organisms.

Moreover, for those degradation products that were tentatively identified in the surface water, the estimated BCFs (BCFBAF v3.01) did not indicate a bioaccumulation potential.

Further details are provided in the confidential annex (not available in published version).

7.7.3.2. **Terrestrial bioaccumulation**

The KOAWIN v1.10 model was used to estimate the log K_{oa} value of DBD (using a log K_{ow} value of 4.0).

Table 14 : Terrestrial bioaccumulation of DBD

Method	Results	Remarks	Reference
Terrestrial bioaccumulation estimate (KOAWIN v1.10)	Log K_{oa} = 16.8	Reliability 3: the log K_{oa} value of 16.8 falls outside the domain range	Registration dossier, (1996b) KOAWIN v1.10

Based on the log K_{ow} value > 2 (log K_{ow} = 4) and the log K_{oa} value > 4.5 (log K_{oa} = 16.8), the screening criterion for terrestrial bioaccumulation is potentially fulfilled for the parent compound DBD.

The terrestrial bioaccumulation potential of the degradation products was not assessed.

7.7.3.3. **Summary and discussion of bioaccumulation**

DBD has a measured log K_{ow} of 4.0, which is close to the cut-off screening value of 4.5 for aquatic bioaccumulation. Moreover, KOWWIN (v1.10) predicts a log K_{ow} of 4.59.

No experimental BCF is available for DBD. QSAR estimates predict a BCF of 25 L/kgwwt (CAESAR QSAR estimate) and 9.24 L/kgwwt (BCFBAF v3.01), which indicates no potential for aquatic bioaccumulation. According to the Arnot-Gobas estimates the BCF and BAF range between 65 (BCF upper trophic) and 90.1 L/kgwwt (BAF lower trophic) when biotransformation is taken into account. Without biotransformation the Arnot-Gobas method estimates a BCF of 1034 L/kgwwt.

The degradation products are probably not bioaccumulative as they are more hydrophilic than DBD (lower retention times in HPLC). Therefore, the log K_{ow}-values of the degradation products will be lower than 4.0 (= experimentally measured value for DBD) and consequently they all screen as not bioaccumulative for aquatic organisms.

Moreover, for those degradation products that were tentatively identified in the surface water, the estimated BCFs (BCFBAF v3.01) did not indicate a bioaccumulation potential.

It is concluded that there is no indication for bioaccumulation in aquatic organisms, neither for the parent compound DBD, nor for its degradation products.

DBD has a bioaccumulation potential in air-breathing organisms, while the bioaccumulation potential for air-breathers was not assessed for the degradation products.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

Only studies related to the aquatic toxicity of the parent substance DBD are reported below (not on the degradation products).

7.8.1.1. **Fish**

7.8.1.1.1. Short-term toxicity to fish

Table 15 : Short-term effects on fish

Method	Results	Remarks	Reference
OECD Guideline 203 (Fish, Acute Toxicity Test) OECD Environment Monograph No. 45 (OECD/GD(92)32) 40 CFR Part 160, 40 CFR Part 792, 21 CFR Part 58 A static test in freshwater with *Oncorhynchus mykiss*	96 h LC_{50} > 10 mg/L (nominal conc.)	Reliability 1 UK Principles of Good Laboratory Practice (The United Kingdom Compliance Programme, Department of Health 1989)	Registration dossier, (1996c) study report
Species: no data freshwater static test WGK (Germany)	96 h LC_0 > 10 000 mg/L test mat. (estimated) based on: behaviour	Reliability 3 summary report performed for German WGK assessment 1989 Non-GLP WAF-study No analytical monitoring	Registration dossier, (1989b) study report

In the 1996 study according to OECD Guideline 203 the test item DBD was added to dimethylformamide and reverse osmosis water with the aid of ultrasonic disruption to form a slurry. The highest attainable nominal test item concentration was 10 mg/L (due to limited solubility of the test material and the amount of auxiliary solvent permitted in the study under the OECD Guidelines) what largely exceeds the water solubility of 48 µg/L. The concentration, homogeneity and stability of the test material in the test solutions were not determined.

The 96h LC_{50}, based on the nominal test concentration is higher than 10 mg/L (above the water solubility of the substance).

7.8.1.1.2. Long-term toxicity to fish

No data available.

7.8.1.2. **Aquatic invertebrates**

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The results are summarised in the following table:

Table 16 : Short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
EU Method C.2 (Acute Toxicity for Daphnia) Static test in freshwater with *Daphnia magna STRAUS parthenogenetic females*	48 h EC_0: > 1 mg/L (nominal conc.)	Reliability 1 key study experimental result GLP Form: powder	Registration dossier, (2008a) study report
OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) EU Method C.2 (Acute Toxicity for Daphnia) Static test in freshwater with *Daphnia magna*	48 h LC_{50} = 0.095 mg/L (immobilisation) 48 h NOEC = 0.056 mg/L (immobilisation)	Reliability 2 GLP No confirmatory analysis performed. Reported effect levels are higher than the reported water solubility of 0.048 mg/L. High levels of co-solvent used: presence of impurities or particulates from micro-emulsion formation could have led to the effects seen. WAF-study	Registration dossier, (1996d) study report

In the 2008 study, no auxiliary solvent was used and undissolved particles were removed from the test medium by filtration. Nominal test item concentration was 1 mg/L but measured test item concentration was below the limit of detection of 0.015 mg/L. No effects were reported.

In the 1996 study, dimethylformamide was used as an auxiliary solvent in the preparation of the test media. An LC_{50} and an NOEC of respectively 0.096 mg/L and 0.056 mg/L are determined. Effects are only seen at a nominal concentrations higher that the water solubility of 0.048 mg/L.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

No data available.

7.8.1.3. **Algae and aquatic plants**

The results are summarised in the following table:

Table 17 : Effects on algae and aquatic plants

Method	Results	Remarks	Reference
OECD Guideline 201 (Alga, Growth Inhibition Test) EU Method C.3 (Algal Inhibition test) Static test with *Scenedesmus subspicatus (new name: Desmodesmus subspicatus)*	72 h ErC_0 > 8 mg/L test	Reliability 2* key study experimental result UK Principles of Good Laboratory Practice (The United Kingdom Compliance Programme, Department of Health 1989) No analytical monitoring Test material was prepared a a slurry in dimethylformamide and reverse osmosis water.	Registration dossier, (1996e) study report
EU Method C.3 (Algal Inhibition test) OECD Guideline 201 (Alga, Growth Inhibition Test) *Desmodesmus subspicatus* (algae)	72 h EC_{50} > 1 mg/L (nominal conc.) 72 h EC_{10} > 1 mg/L (nominal conc.) 72 h NOErC >1 mg/L (nominal conc.)	Reliability 1 key study experimental result Deviations : - Cell density at test start was 5000 cells/mL - 6 replicates were tested for the test item concentration 1.0 mg/L.	Registration dossier, (2008b) study report

*the study is given reliability 1 by the registrant(s), but eMSCA considers it reliability 2 due to the absence of analytical monitoring

No effects are observed up to the water solubility.

7.8.1.4. **Sediment organisms**

No data available.

7.8.1.5. Other aquatic organisms

Table 18 : Effects on micro-organisms

Method	Results	Remarks	Reference
ISO/TC/147/SC 5N 76 "Determination of the inhibitory effect of water constituents on bacteria (Pseudomonas cekk multiplication inhibition te8st)" OECD Environment Monograph No. 45 (OECD/GD(92)32) directives 87/18/EEC and Pseudomonas putida 88/320/EEC static test with freshwater German Water Hazard Classification Scheme ("Bewertung Wassergefärdender Stoffe" - Herausgegeben vom Umweltbundesamt, Sepember 1979 LTWS - Nr. 10)	16 h EC_0 > 8 mg/L test (growth inhibition)	Reliability 1 key study experimental result UK Principles of Good Laboratory Practice (The United Kingdom Compliance Programme, Department of Health 1989)	Registration dossier, (1996f) study report
equivalent or similar to OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) static test in freshwater with activated sludge	3 h EC_0 > 1000 mg/L (nominal conc.) (respiration rate)	Reliability 2 2 Non-GLP	Registration dossier, (1986) study report

No effects are observed up to the water solubility.

7.8.2. Terrestrial compartment

No data available.

7.8.3. Microbiological activity in sewage treatment systems

No data available.

7.8.4. PNEC derivation and other hazard conclusions

As no effects where seen in the aquatic tests with DBD up to the water solubility, no relevant PNEC could be calculated for the water, sediment or soil compartments.

7.8.5. Conclusions for classification and labelling

Table 19 : Summary of comparison with the CLP criteria for the environment

Endpoint	Classification criteria	Results	Conclusion
Degradation	The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70 % DOC removal or 60 % theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation. The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life < 16 days (corresponding to a degradation of > 70% within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment.	DBD is not readily degradable DBD does not ultimately degrade in surface water DBD is quickly primarily degraded, half-life = 1 d, but some of the degradation products are persistent. No information available on the aquatic toxicity of the degradation products.	DBD is **not rapidly degradable**
Bioaccumulation	If BCF available > 500: the substance meets the criterion If no BCF available and log K_{ow} ≥ 4: The substance meets the criterion	No experimental BCF is available, but the estimated value (using the measured log K_{ow} of 4) is well below 500	DBD does **not** meet the criterion for aquatic **bioaccumulation**
Acute Aquatic toxicity	LC/EC_{50} ≤ 1 mg/L	Most sensitive species: *Daphnia magna* with an 48 h EC_{50} = 0.095 mg/L (Immobilisation), but no effect up to the WS (0.048 mg/L)	No effect up to the WS **No classification**
Chronic toxicity	Classification based on Table 4.1.0 (b)(ii) and Table 4.1.0 (b)(iii) of the CLP-regulation • Table 4.1.0 (b)(i) : Not rapidly degradable substance:	• Table 4.1.0 (b) (i):	**Aquatic Chronic 4, H413**

	<u>Category Chronic 1</u>: Chronic NOEC or ECx ≤ 0.1 mg/L **<u>Category Chronic 2</u>**: Chronic NOEC or ECx ≤ 1 mg/L • Table 4.1.0 (b)(iii) : Not rapidly degradable and/or BCF ≥ 500 (or log K_{ow} ≥ 4), AND **<u>Category Chronic 1</u>**: Acute EC_{50} ≤ 1mg/L **<u>Category Chronic 2</u>** : Acute EC_{50} > 1 to ≤ 10 mg/L **<u>Category Chronic 3</u>** : Acute EC_{50} > 10 to ≤ 100 mg/L Take most stringent outcome • **<u>Category Chronic 4</u>** The substance is poorly soluble, is not rapidly degradable and has a BCF≥500 or log Kow≥4, unless NOEC for all trophic levels >WS>1mg/L	*72 h NOErC (algae): >1 mg/L* *No effect up to WS (0.048 mg/L)* **No classification** • <u>Table 4.1.0 (b) (iii) :</u> Not rapidly degradable AND log K_{ow} = 4 AND EC_{50} of most sensitive species *Daphnia magna* is 0.095 mg/L (48h, Immobilisation) ⇨ No effect up to the WS (0.048 mg/L) **No classification** • WS = 0.048 mg/L + log K_{ow} = 4 + only an NOEC for algae	

7.9. Human Health hazard assessment

Not evaluated.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and vPvB assessment

7.11.1. Persistence

The substance DBD is not readily biodegradable but degrades rapidly in surface water, with a half-life of 1 day (primary degradation). Several degradation products are formed and for some of them the chemical structure was tentatively identified, although definitive proof of the chemical identity cannot be provided. A kinetic analysis of the simulation study in water demonstrates that some of these degradation products meet the P and even the vP criterion in freshwater.

It is concluded that DBD itself is not persistent, but that some of its degradation products are stable and fulfil the P/vP criterion in freshwater.

7.11.2. Bioaccumulation

DBD has a measured log K_{ow} of 4.0.

QSAR estimates predict a BCF of 25 L/kgwwt (CAESAR QSAR estimate) and 9.24 L/kgwwt (BCFBAF v3.01). According to the Arnot-Gobas estimates the BCF and BAF range between 65 (BCF upper trophic) and 90.1 L/kgwwt (BAF lower trophic) when biotransformation is taken into account. Not considering biotransformation the Arnot-Gobas method estimates a BCF of 1034 L/kgwwt.

Therefore, the B criterion for aquatic organisms is probably not fulfilled for the parent compound DBD.

The degradation products do not show a potential to bioaccumulate in aquatic organisms.

7.11.3. Toxicity

Human Health
Not assessed.

Environment
In the various toxicity studies with aquatic organisms, no effects were seen up to the water solubility of 0.048 mg/L. Aquatic toxicity of the degradation products was not assessed.

7.11.4. Overall conclusion

The eMSCA concludes that N,N'-dithiodi-o-phenylenedibenzamide (DBD) is not a PBT/vPvB substance as neither the parent compound nor the degradation products meet the Annex XIII criteria both for persistence and for bioaccumulation.

Based on the available data there is no indication that the toxicity criterion is fulfilled, but the T criterion was not fully assessed (neither for the parent compound nor the degradation products) as the parent compound is not persistent and the degradation products show no potential to bioaccumulate.

7.12. Exposure assessment

Exposure was not assessed in this substance evaluation.

7.13. Risk characterisation

Risk characterisation was not assessed in this substance evaluation.

7.14. References

See ECHA's dissemination website for the registration dossier study reports.

7.15. Abbreviations

B :	bioaccumulative
BAF :	bioaccumulation factor
BCF :	bioconcentration factor
CA :	Competent Authority
C&L :	Classification & Labelling
CLP :	Classification, Labelling and Packaging
Conc. :	concentration
CoRAP :	Community Rolling Action Plan
DAT :	days after treatment
DBD :	N,N'-dithiodi-o-phenylenedibenzamide
DT_{50} :	disappearance time-50; time that half of the test item disappears
EC :	effect concentration
ECHA :	European Chemicals Agency
eMSCA :	evaluating Member State Competent Authority
EU :	European Union
HAT :	hours after treatment
GLP :	Good Laboratory Practice
LC :	lethal concentration
NOAEL :	No Observed Adverse Effect Level
NOEC :	No Observed Effect Concentration
OECD :	Organisation for Economic Co-operation and Development
P :	persistent
PBT :	Persistent, Bioaccumulative and Toxic
PEC :	Predicted Environmental Concentration
PNEC :	Predicted No Effect Concentration
QSAR :	Quantitative Structure-Activity Relationship
REACH :	Regulation No 1907/2006 concerning Registration, Evaluation, Authorisation and Restriction of Chemicals
SVHC :	Substance of Very High Concern

T : toxic

TG : Test Guideline

Confidential annex is removed from this public version.