REACH

# Thiodiethylene bis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]

EC number: 255-392-8 | CAS number: 41484-35-9

Environmental fate & pathways

## Bioaccumulation: aquatic / sediment

S-01 | Summary

## Administrative data

## Link to relevant study record(s)

### Reference

#### Reference 1

| | |
|---|---|
| Endpoint: | bioaccumulation in aquatic species: fish |
| Type of information: | experimental study |
| Adequacy of study: | supporting study |
| Study period: | 1998-05-01 to 1998-09-30 |
| Reliability: | 2 (reliable with restrictions) |
| Rationale for reliability incl. deficiencies: | other: study conducted according to OECD guideline but not GLP-compliant |
| Qualifier: | according to guideline |
| Guideline: | OECD Guideline 305 C (Bioaccumulation: Test for the Degree of Bioconcentration in Fish) |
| Version / remarks: | 1981 |
| Deviations: | yes |
| Remarks: | test water analyzed once a week instead of twice |
| GLP compliance: | no |
| Radiolabelling: | no |
| Details on sampling: | - Sampling intervals/frequency for test organisms: 1st, 2nd, 3rd, 4th, 6th, 8th week<br>- Sampling intervals/frequency for test medium samples: once a week |
| Vehicle: | not specified |
| Details on preparation of test solutions, spiked fish food or sediment: | PREPARATION AND APPLICATION OF TEST SOLUTION<br>- Method: The test substance was introduced continuously to maintain constant concentration. |
| Test organisms (species): | Cyprinus carpio |
| Details on test organisms: | TEST ORGANISM<br>- Common name: Japanese carp |

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| | - Strain: Cyprimus carpio<br>- Length at study initiation: 9.7 ± 0.5 cm<br>- Weight at study initiation: 23.9 ± 3.3 g<br>- Description of housing/holding area: glass aquarium (100 L) |
| Route of exposure: | aqueous |
| Test type: | flow-through |
| Water / sediment media type: | natural water: freshwater |
| Total exposure / uptake duration: | 8 wk |
| Hardness: | no data |
| Test temperature: | 25.2 ± 0.5 °C |
| pH: | no data |
| Dissolved oxygen: | 7.1 - 7.4 mg/L |
| TOC: | no data |
| Details on test conditions: | TEST SYSTEM<br>- Test vessel: glass aquarium<br>- Size: 100 L<br>- Renewal rate of test solution: flow rate: 432 L/day |
| Nominal and measured concentrations: | nominal: 1 and 0.1 mg/L |
| Reference substance (positive control): | no |
| Details on estimation of bioconcentration: | BASIS FOR CALCULATION OF BCF<br>BCF was calculated as the ratio of the concentration of test substance between fish and the exposure water taken periodically for analysis. |
| Lipid content: | > 4.1 - < 4.5 % |
| Time point: | start of exposure |
| Type: | BCF |
| Value: | > 60 - < 223 dimensionless |
| Basis: | not specified |
| Calculation basis: | steady state |
| Remarks on result: | other: Conc.in environment / dose:1 mg/L |
| Type: | BCF |
| Value: | > 121 - < 532 dimensionless |
| Basis: | not specified |
| Calculation basis: | steady state |
| Remarks on result: | other: Conc.in environment / dose:0.1 mg/L |
| Metabolites: | not determined |

## Reference 2

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|---|---|
| Endpoint: | bioaccumulation in aquatic species: fish |
| Type of information: | (Q)SAR |
| Adequacy of study: | supporting study |
| Study period: | 2017 |
| Reliability: | 2 (reliable with restrictions) |
| Rationale for reliability incl. deficiencies: | results derived from a valid (Q)SAR model, but not (completely) falling into its applicability domain, with adequate and reliable documentation / justification |
| Justification for type of information: | 1. SOFTWARE<br>OASIS Catalogic v5.12.1<br><br>2. MODEL (incl. version number)<br>BCF base-line model v02.09 - July 2016<br><br>3. SMILES OR OTHER IDENTIFIERS USED AS INPUT FOR THE MODEL |

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| | See section 'Test Material'.<br><br>4. SCIENTIFIC VALIDITY OF THE (Q)SAR MODEL<br>See attached QMRF.<br><br>5. APPLICABILITY DOMAIN<br>See attached QPRF.<br><br>6. ADEQUACY OF THE RESULT<br>- The model is scientifically valid (see attached QMRF).<br>- The model estimates the Bioconcentration factor (BCF) as required information point according to Regulation (EC) No 1907/2006 [REACH], Annex IX, 9.3.2 Bioaccumulation in aquatic species (preferably fish);<br>further related predictions: Apparent effect of mitigating factors / Maximum bioconcentration factor (BCFmax) / Maximum diameter of energetically stable conformers / Whole body primary biotransformation half-life / Metabolic biotransformation rate constant Km / Metabolites and their quantitative distribution<br>- See attached QPRF for reliability assessment. |
| Principles of method if other than guideline: | Calculation using Catalogic v.5.12.1, BCF base-line model v.02.09 |
| GLP compliance: | no |
| Details on estimation of bioconcentration: | BASIS FOR CALCULATION OF BCF<br>- Estimation software: OASIS Catalogic v5.12.1 [BCF base line model - v.02.09] |
| | Key result |
| Type: | BCF |
| Value: | 13.2 L/kg |
| Remarks on result: | other: considering all mitigating factors; the substance is not within the applicability domain of the model. |
| Type: | BCF |
| Value: | 3 581 L/kg |
| Remarks on result: | other: without considering any mitigating factors; the substance is not within the applicability domain of the model. |

## Reference 3

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| Endpoint: | bioaccumulation in aquatic species: fish |
| Type of information: | (Q)SAR |
| Adequacy of study: | weight of evidence |
| Study period: | 2017 |
| Reliability: | 2 (reliable with restrictions) |
| Rationale for reliability incl. deficiencies: | results derived from a valid (Q)SAR model, but not (completely) falling into its applicability domain, with adequate and reliable documentation / justification |
| Justification for type of information: | 1. SOFTWARE<br>OASIS Catalogic v5.11.19<br><br>2. MODEL (incl. version number)<br>BCF base-line model v02.09 - July 2016<br><br>3. SMILES OR OTHER IDENTIFIERS USED AS INPUT FOR THE MODEL<br>See section 'Test Material'.<br><br>4. SCIENTIFIC VALIDITY OF THE (Q)SAR MODEL<br>See attached QMRF.<br><br>5. APPLICABILITY DOMAIN<br>See attached QPRF.<br><br>6. ADEQUACY OF THE RESULT<br>- The model is scientifically valid (see attached QMRF).<br>- The model estimates the Bioconcentration factor (BCF) as required information point according to Regulation (EC) No 1907/2006 [REACH], Annex IX, 9.3.2 Bioaccumulation in aquatic species (preferably fish);<br>further related predictions: Apparent effect of mitigating factors / Maximum bioconcentration factor (BCFmax) / Maximum diameter of energetically stable conformers / Whole body primary biotransformation half-life / Metabolic biotransformation rate constant Km / Metabolites and their quantitative distribution<br>- See attached QPRF for reliability assessment. |
| Principles of method if other than guideline: | Calculation using Catalogic v.5.11.19, BCF base-line model v.02.09 |
| GLP compliance: | no |
| Details on estimation of bioconcentration: | BASIS FOR CALCULATION OF BCF<br>- Estimation software: OASIS Catalogic v5.11.19 [BCF base line model - v.02.09] |
| | Key result |
| Type: | BCF |

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| Value: | 7.4 L/kg |
| Remarks on result: | other: considering all mitigating factors; the substance is not within the applicability domain of the model. |
| Type: | BCF |
| Value: | 165.6 L/kg |
| Remarks on result: | other: without considering any mitigating factors; the substance is not within the applicability domain of the model. |

## Reference 4

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| Endpoint: | bioaccumulation: aquatic / sediment |
| Type of information: | (Q)SAR |
| Adequacy of study: | weight of evidence |
| Reliability: | 2 (reliable with restrictions) |
| Rationale for reliability incl. deficiencies: | accepted calculation method |
| Principles of method if other than guideline: | Estimation of BCF, BAF and biotransformation rate using BCFBAF v3.01 |
| GLP compliance: | no |
| Test organisms (species): | other: fish |
| Details on estimation of bioconcentration: | BASIS INFORMATION<br>- Calculated logPow: 10.4<br><br>BASIS FOR CALCULATION OF BCF<br>- Estimation software: BCFBAF v3.01 |
| Type: | BCF |
| Value: | 45.7 L/kg |
| Basis: | not specified |
| Remarks on result: | other: The substance is within the molecular weight and logKow ranges of the applicability domain of the BCFBAF submodel: Bioconcentration factor (BCF; Meylan et al., 1997/1999). One of the fragments for the correction factors was exceeded. |
| Type: | BCF |
| Value: | 0.911 L/kg |
| Basis: | not specified |
| Calculation basis: | steady state |
| Remarks on result: | other: Upper trophic, incl. biotransformation estimates; Mol. weight within range of training set but exceeding 600 g/mol. logKow outside range of training set. |
| Type: | BCF |
| Value: | 37.91 L/kg |
| Calculation basis: | steady state |
| Remarks on result: | other: Upper trophic, incl. biotransformation estimates of zero; Mol. weight within range of training set but exceeding 600 g/mol. logKow outside range of training set. |
| Details on kinetic parameters: | Biotransformation half-life (days): 0.2075<br>Biotransformation rate (kM, normalised to 10 g fish at 15 °C): 3.341/day<br>The substance is not within the applicability domain of the BCFBAF submodel: Biotransformation rate in fish (kM; Arnot et al., 2008a/b). Mol. weight is within the range of the training set but exceeding 600 g/mol; logKow is outside the range of the training set. |

Summary Results:

Log BCF (regression-based estimate): 1.66 (BCF = 45.7 L/kg wet-wt)

Biotransformation Half-Life (days) : 0.207 (normalized to 10 g fish)

Log BAF (Arnot-Gobas upper trophic): -0.04 (BAF = 0.913 L/kg wet-wt)

Log Kow (experimental): not available from database

Log Kow used by BCF estimates: 10.36

Equation Used to Make BCF estimate:

Log BCF = -0.49 log Kow + 7.554 + Correction

Correction(s): Value

Tert-Butyl ortho-phenol type -0.222

Alkyl chains (8+ -CH2- groups) -0.596

Estimated Log BCF = 1.660 (BCF = 45.72 L/kg wet-wt)

Whole Body Primary Biotransformation Rate Estimate for Fish:

| TYPE | NUM | Log Biotransformation fragment description | COEFF | VALUE |
|---|---|---|---|---|
| Frag | 2 | Aromatic alcohol [-OH] | -0.4727 | -0.9455 |
| Frag | 2 | Ester [-C(=O)-O-C] | -0.7605 | -1.5211 |
| Frag | 4 | Carbon with 4 single bonds & no hydrogens | -0.2984 | -1.1937 |
| Frag | 2 | Alkyl substituent on aromatic ring | 0.1781 | 0.3561 |
| Frag | 2 | Aromatic-CH2 | -0.3365 | -0.6730 |
| Frag | 4 | Aromatic-H | 0.2664 | 1.0655 |
| Frag | 12 | Methyl [-CH3] | 0.2451 | 2.9413 |
| Frag | 6 | -CH2- [linear] | 0.0242 | 0.1451 |
| Frag | 2 | Benzene | -0.4277 | -0.8555 |
| L Kow | * | Log Kow = 10.36 (KowWin estimate) | 0.3073 | 3.1834 |
| MolWt | * | Molecular Weight Parameter | | -1.6487 |
| Const | * | Equation Constant | | -1.5371 |
| RESULT | LOG Bio Half-Life (days) | | | -0.6831 |
| RESULT | Bio Half-Life (days) | | | 0.2075 |
| NOTE | Bio Half-Life Normalized to 10 g fish at 15 deg C | | | |

Biotransformation Rate Constant:
kM (Rate Constant): 3.341 /day (10 gram fish)
kM (Rate Constant): 1.879 /day (100 gram fish)
kM (Rate Constant): 1.057 /day (1 kg fish)
kM (Rate Constant): 0.5941 /day (10 kg fish)

Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
Estimated Log BCF (upper trophic) = -0.040 (BCF = 0.9111 L/kg wet-wt)
Estimated Log BAF (upper trophic) = -0.040 (BAF = 0.9128 L/kg wet-wt)
Estimated Log BCF (mid trophic) = -0.019 (BCF = 0.9564 L/kg wet-wt)
Estimated Log BAF (mid trophic) = 0.040 (BAF = 1.096 L/kg wet-wt)
Estimated Log BCF (lower trophic) = -0.014 (BCF = 0.9676 L/kg wet-wt)
Estimated Log BAF (lower trophic) = 0.386 (BAF = 2.43 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
Estimated Log BCF (upper trophic) = 1.579 (BCF = 37.91 L/kg wet-wt)
Estimated Log BAF (upper trophic) = 5.274 (BAF = 1.878e+005 L/kg wet-wt)

## Reference 5

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| Endpoint: | bioaccumulation: aquatic / sediment |
| Type of information: | (Q)SAR |
| Remarks: | Migrated phrase: estimated by calculation |
| Adequacy of study: | weight of evidence |
| Reliability: | 2 (reliable with restrictions) |
| Rationale for reliability incl. deficiencies: | results derived from a valid (Q)SAR model, but not (completely) falling into its applicability domain, with adequate and reliable documentation / justification |
| Principles of method if other than guideline: | T.E.S.T. is a toxicity estimation software tool. The program requires only the molecular structure of the test item, all other molecular descriptors which are required to estimate the toxicity are calculated within the tool itself. The molecular descriptors describe physical characteristics of the molecule (e.g. E-state values and E-state counts, constitutional descriptors, topological descriptors, walk and path counts, connectivity, information content, 2d autocorrelation, Burden eigenvalue, molecular property (such as the octanol-water partition coefficient), Kappa, hydrogen bond acceptor/donor counts, molecular distance edge, and molecular fragment counts). Each of the available methods uses a different set of these descriptors to estimate the toxicity.<br>The bioaccumulation factor (BCF) was estimated using several available methods: hierarchical clustering method; FDA method, single model method; group contribution method; nearest neighbor method; consensus method. The methods were validated using statistical external validation using separate training and test data sets. |

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| | The experimental data set was obtained from several different databases (Dimitrov et al., 2005; Arnot and Gobas, 2006; EURAS; Zhao, 2008). From the available data set salts, mixtures and ambiguous compounds were removed. The final data set contained 676 chemicals.<br><br>References:<br>- Dimitrov, S., N. Dimitrova, T. Parkerton, M. Combers, M. Bonnell, and O. Mekenyan. 2005. Base-line model for identifying the bioaccumulation potential of chemicals. SAR and QSAR in Environmental Research 16:531-554.<br>- Arnot, J.A., and F.A.P.C. Gobas. 2006. A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms. Environ. Rev. 14:257-297.<br>- EURAS. Establishing a bioconcentration factor (BCF) Gold Standard Database. EURAS [cited 5/20/09]. Available from http://www.euras.be/eng/project.asp?ProjectId=92.<br>- Zhao, C.; Boriani, E.; Chana, A.; Roncaglioni, A.; Benfenati, E. 2008. A new hybrid system of QSAR models for predicting bioconcentration factors (BCF). Chemosphere 73:1701-1707. |
| GLP compliance: | no |
| Test organisms (species): | other: fish |
| Details on estimation of bioconcentration: | BASIS FOR CALCULATION OF BCF<br>- Estimation software: US EPA T.E.S.T. v4.2.1<br><br>Applied estimation methods:<br>- Hierarchical clustering<br>- FDA<br>- Single model<br>- Group contribution<br>- Nearest neighbor<br>- Consensus |
| | Key result |
| Type: | BCF |
| Value: | 143.13 dimensionless |
| Remarks on result: | other: method: consensus (average of reasonable results from all models); log BCF = 2.16; Based on the mean absolute error, the confidence in the predicted BCF values is low. |

## Description of key information

Does not significantly accumulate in aquatic organisms.

### Key value for chemical safety assessment

## Additional information

In Article 13 of Regulation (EC) No 1907/2006, it is laid down that information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI (of the same Regulation) are met. Furthermore, according to Article 25 of the same Regulation testing on vertebrate animals shall be undertaken only as a last resort.

According to Annex XI of Regulation (EC) No 1907/2006 (Q)SAR results can be used if (1) the scientific validity of the (Q)SAR model has been established, (2) the substance falls within the applicability domain of the (Q)SAR model, (3) the results are adequate for the purpose of classification and labeling and/or risk assessment and (4) adequate and reliable documentation of the applied method is provided.

For the assessment of CAS 32687-78-8 (Q)SAR results were used for bioaccumulation. The criteria listed in Annex XI of Regulation (EC) No 1907/2006 are considered to be adequately fulfilled and therefore the endpoint(s) sufficiently covered and suitable for risk assessment.

Therefore, and for reasons of animal welfare, further experimental studies on bioaccumulation are not provided.

Assessment for CAS 41484 -35 -9

The bioaccumulative potential of the substance was assessed in a weight of evidence approach including several QSAR calculations as well as information on the molecular dimensions.

The following QSAR tools have been used:

(1) Catalogic v5.11.19, BCF base-line model v02.09

(2) US EPA EPISuite v4.11, BCFBAF v3.01

(3) US EPA T.E.S.T. v4.2.1

(4) Vega v1.1.3 including CAESAR v2.1.14, Meylan v1.0.3 and Read-across/KNN v1.1.0

Regarding the reliability of the QSAR predictions the results from the models included in the Vega tool were not considered for the general prediction because the substance was not within the applicability domain of the model.

The domain of the BCF base-line model implemented in Catalogic is divided in three sub-domains. (1) The parameter domain which compares the logKow, water solubility and molecular size of the substance to the specific ranges of the training set, (2) the structural fragment domain which compares the atom-centered fragments of the substance to the ones from the training set and (3) the mechanistic domain which evaluates the general uptake mechanism of the compound as only such chemicals which are taken up by passive diffusion can be predicted. The current substance was

within the parameter and the mechanistic domain of the model. In regards to the structural domain, 85.71% of the fragments of the substance could be found in correctly predicted training chemicals. Only 14.29% of the fragments were not present in the training chemicals. Principally, the substance is not within the domain of the model as not all atom-centered fragments could be found in correctly predicted training chemicals, however, the result is regarded as reliable and adequate for the use in a weight of evidence approach. The predicted BCF value was determined to be 7.4 L/kg. Metabolism, size and to a minor extent water solubility were the most important mitigating factors decreasing the BCF value.

The US EPA's EPISuite includes a regression-based BCF prediction and a prediction taking the biotransformation rate into account. Concerning the regression based prediction the compound was within the molecular weight and logKow ranges of the model. However, the maximum number of fragments was exceeded in one instance as the compound comprises two tert-butyl ortho phenol groups instead of one. Therefore, the result might be less reliable. Nevertheless, the result of the regression-based estimation was regarded as adequate in a weight of evidence approach. The model predicted the BCF with 45.7 L/kg. The second model takes the biotransformation of the compound into account. The substance was not within the applicability domain. A BCF of 0.9111 L/kg (upper trophic level, incl. biotransformation rates) was estimated. As the compound was not within the domain of the second model it was not taken into account for the final assessment.

US EPA's T.E.S.T. model combines 5 methods in the consensus approach. The model only delivers results if the substance is in the applicability domain of the respective model. The compound was in domain of all the models included in the T.E.S.T. package with the exception of the Group Contribution model. However, the confidence of the results is low due to the mean absolute error of the single results. Nevertheless, the results were regarded as reliable in a weight of evidence approach. The consensus approach resulted in a BCF value of 143.13.

In addition to the experimental and modelled BCF data, information on the molecular dimensions were used. According to ECHA's Guidance on Information Requirements and Chemical Safety Assessment, R.11: PBT Assessment, the capability of crossing biological membranes is hindered if the average maximum diameter is > 1.7 nm. The present substance has an average maximum diameter of 2.3 nm. Therefore, an uptake through biological membranes is not expected.

In conclusion, in a weight of evidence approach using all available data, it can be concluded that the substance does not significantly accumulate in organisms.

Assessment for the main metabolite of CAS 41484-35-9

According to the results of Catalogic v5.11.19, CATALOGIC 301C v.09.13 the main metabolite during degradation is CAS 20170-32-5. To further assess the bioaccumulative potential of CAS 20170-32-5 Catalogic v5.12.1, BCF base-line model v02.09 together with the results of an experimentel study were used.

In the experimental study Japanese carp (Cyprinus carpio) were exposed to the test substance in 2 different concentrations (1 and 0.1 mg/L) for a test duration of 8 weeks in a flow-through test procedure. The test water was analyzed weekly, the concentration of the test substance in fish was determined in weeks 1, 2, 3, 4, 6 and 8 to calculate the BCF value. The determined BCF values were 60 -223 for the lower and 121-532 for the higher test concentration.

The compound is within the parameter ranges of the QSAR model, i.e. its water solubility, molecular weight and lowKow are within the ranges of the training set. It needs to be pointed out, that the prediction was conducted with the neutral molecule and the logKow of the neutral molecule. The compound is also within the mechanistic domain, i.e. the compound is taken up by passive diffusion only. Furthermore, CAS 20170-32-5 is within the structural domain by 86.67%. Only 13.33% of the fragments not present in the training set.

The model predicted a BCF of 13.2 L/kg with all mitigating factors applied. The most influential mitigating factors were size, metabolism and acids.

As the substance has a carboxylic acid moiety and a predicted pKa of 4.74 (SPARC accessed on November 13$^{th}$, 2017) it is mostly present in its anionic form under environmental conditions (pH 5 to 9). Since the neutral and ionic species exhibit different polarities, the logKow value is pH dependent. Therefore, the logD was calculated. It ranges from 3.8 at pH 5 to 0.2 at pH 9 which is well below the B threshold screening criterion of 4.5.

In summary, due to the experimental and predicted BCF values and the logD of << 4.5 the substance is expected to be significantly below the B threshold of 2000.