Substance Name: Bumetrizole (UV-326)

EC Number: 223-445-4

CAS Number: 3896-11-5

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF

Bumetrizole (UV-326)

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS VPVB (ARTICLE 57(E)) PROPERTIES

Adopted on 13 December 2023

Note

The Annex XV dossier that was submitted by Germany covers both the substances UV-326 and UV-329. However, for each substance a separate support document has been created for their identification as a substance of very high concern. The present support document may therefore contain some redundant references to the other substance in the sections describing the underlying scientific data.

THIS DOCUMENT HAS BEEN PREPARED ACCORDING TO TEMPLATE: TEM-0049.04

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ABBREVIATIONS

AR: applied radioactivity
B: bioaccumulative (pertaining to REACH Annex XIII)
BAF: bioaccumulation factor
BCF: bioconcentration factor
BCF_K: kinetic bioconcentration factor
BCF_{KL}: lipid-normalised kinetic bioconcentration factor
BCF_{KgL}: lipid-normalised growth corrected kinetic bioconcentration factor
BCF_{ss}: steady-state bioconcentration factor
BCF_{ssL}: lipid-normalised steady-state bioconcentration factor
BMF: biomagnification factor
BMF_{Kg}: growth-corrected kinetic biomagnification factor
BOD: biochemical oxygen demand
bw: body weight
CAS RN: CAS registry number
C_f: test substance concentration in fish
C_w: test substance concentration in water
CLH: Harmonised classification and labelling
CLP: Classification, labelling, and packaging of substances
DF: detection frequency
DMEL: Derived minimum effect level
DNEL: Derived no-effect level
DT50: half-life
DegT50 degradation half-life
dw: dry weight
EC: effect concentration
es-BANK: Environmental Specimen Bank of Ehime University
GC-HRMS: gas chromatography/ high resolution mass spectrometry
GC/MS: gas chromatography/ mass spectrometry
GC-MS/MS: gas chromatography tandem mass spectrometry
GLP: good laboratory practice
H. Azteca: *Hyalella Azteca*
HPLC: high performance liquid chromatography
HYBIT: *Hyalella Azteca* Bioconcentration Test
IB: Iles des Boucherville
IUCN: International Union for Conservation of Nature
IV: Iles Vert
k_1: uptake rate constant
k_2: depuration rate constant
k_{2g}: growth corrected depuration rate constant
K: Kaveri River, India
K_{OA}: octanol-air partition coefficient
K_{OW}: octanol-water partition coefficient
LSL: Lake St. Louis, Montreal
LC50: Lethal concentration to 50% of test animals
LC-HRMS: liquid chromatography/ high resolution mass spectrometry
LC-MS/MS: liquid chromatography tandem mass spectrometry
LOD: limit of detection
LOEC: lowest observed effect concentration
LOQ: limit of quantification
lw: lipid weight
M1: 3-[3-(2*H*-1,2,3-benzotriazol-2-yl)-5-*tert*-butyl-4-hydroxyphenyl]propanoic acid (EC 630-348-4)
MDL: method detection limit
MSC: Member State Committee

MQL: method quantification limit
NA: not analysed
ND: not detected
NER: non-extractable residues
NOAEC: No observed adverse effect concentration
NO(A)EL: no observed (adverse) effect level
NOEC: no observed effect concentration
OEL: occupational exposure limit
P: Persistence (pertaining to REACH Annex XIII) or persistent
PBT: persistent, bioaccumulative, and toxic
PLE: pressurised liquid extraction
(Q)SAR: (quantitative) structure-activity relationship
R2: coefficient of determination
RAC: Committee for Risk Assessment
RMSE: Root Mean Square Error
SAR: structure-activity relationship
SEV: Substance Evaluation
SFO: Single First Order
SVHC: Substance of very high concern
STOT RE: Specific Target Organ Toxicity – Repeated exposure
T: Toxic (pertaining to REACH Annex XIII)
TG: Test guideline
TGR: Transgenic rodent
TMF: Trophic magnification factor
TOC: total organic carbon
TWA: time weighted average
UPLC-MS/MS: ultra-high performance liquid chromatography tandem mass spectrometry
UM-PPS: University of Minnesota Biocatalysis/Biodegradation Prediction System
UV-320: 2-benzotriazol-2-yl-4,6-di-*tert*-butylphenol (EC 223-346-6)
UV-326: Bumetrizole, 2-*tert*-butyl-6-(5-chloro-2*H*-benzotriazol-2-yl)-4-methylphenol (EC 223-445-4)
UV-327: 2,4-di-*tert*-butyl-6-(5-chlorobenzotriazol-2-yl)phenol (EC 223-383-8)
UV-328: 2-(2*H*-benzotriazol-2-yl)-4,6-ditertpentylphenol (EC 247-384-8)
UV-329: 2-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol (EC 221-573-5)
UV-350: 2-(2*H*-benzotriazol-2-yl)-4-(*tert*-butyl)-6-(sec-butyl)phenol (EC 253-037-1)
UV-384: A mixture of branched and linear C7-C9 alkyl 3-[3-(2*H*-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxyphenyl]propionates (EC 407-000-3)
UV-P: 2-(2*H*-benzotriazol-2-yl)-p-cresol (EC 219-470-5)
V: Vellar River, India
vB: very bioaccumulative (pertaining to REACH Annex XIII)
vP: very persistent (pertaining to REACH Annex XIII)
vPvB: very persistent and very bioaccumulative (pertaining to Annex XIII REACH)
WoE: weight-of-evidence
ww: wet weight

IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance name: Bumetrizole (UV-326)

EC number: 223-445-4

CAS number: 3896-11-5

- The substance is identified as very persistent and very bioaccumulative (vPvB) according to Article 57 (e) of Regulation (EC) No 1907/2006 (REACH).

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

A weight of evidence determination according to the provisions of Annex XIII of REACH has been used to identify UV-326 as a vPvB substance. All available relevant information (such as the results of standard tests, monitoring and modelling, information from the application of the read-across and (Q)SAR results) was considered together in a weight-of-evidence approach.

Persistence

The screening criterion for persistence (P) is fulfilled for UV-326. The results from the available screening studies (reliable with or without restrictions) showed that this substance is not readily biodegradable. This is confirmed by the available (Q)SAR results with BIOWIN and CATALOGIC which indicate that UV-326 screens as potentially P or vP. The outcomes of the screening tests and the (Q)SARs predictions have been assigned a low weight in the weight-of-evidence approach (WoE) for the P assessment.

Hydrolysis of UV-326 is not expected due to the absence of functional groups susceptible to hydrolysis. As a conclusion, abiotic degradation of UV-326 is not considered to be a significant degradation pathway in the environment.

In a water-sediment simulation study for UV-326 at 20 °C (reliable with restrictions), no degradation was observed after 100 days. At an environmentally relevant temperature of 12 °C this corresponded to a half-life significantly larger than 212 days for UV-326 thus indicating its very persistent properties in sediment (DegT50>180 days). The outcome of this higher tier study is given a high weight in the WoE approach as it provides information directly comparable with the P and vP criteria set out in Annex XIII, points 1.1.1 (d) and 1.2.1 (b) of the REACH Regulation.

Faster dissipation of UV-326 in an aquifer test (reliable with restrictions) may be related to the different test conditions and the studied compartment compared to an OECD water-sediment simulation study. This study has been assigned a low weight in the WoE approach considering the studied compartment, the test conditions and the difficulty to derive an appropriate DT50. Simulation test results (reliable with restrictions) for a structurally related substance 3-[3-(2*H*-benzotriazol-2-yl)-5-*tert*-butyl-4-hydroxyphenyl]propionicacid (M1) *H*-support both very high persistence in sediment (DegT50 in sediment >180 days) for UV-326 and the impact of different sediment types on dissipation. This study on a structurally related substance is assigned a medium weight in the WoE approach.

UV-326 and further phenolic benzotriazoles have been detected in sediment cores that date back years and even decades (starting from the 1960s), both in samples downstream from a former point source and in samples from urban estuaries. This information provides indirect evidence that UV-326 can persist in sediments for several decades. Monitoring data in sediment cores are used as supporting information in the WoE approach for UV-326. They are in line with the outcome of the water-sediment simulation study, the screening studies and the QSAR predictions as they point towards the persistence of UV-326 in sediments.

UV-326 is persistent (and potentially very persistent) in two soil dissipation studies (reliable with restrictions) (at least DegT50>120 days).

As an overall conclusion, based on the above information used in a weight-of-evidence-approach, it is concluded that UV-326 meets the 'persistence' criterion (P) and the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and very persistent (P/vP) properties in sediment (DegT50 > 180 days). Furthermore, UV-326 meets the 'persistence' criterion (P) and potentially the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and potentially its very persistent (P/vP) properties in soil (at least DegT50 > 120 days).

Bioaccumulation

UV-326 screens as potentially B/vB due to the available log K_{ow} values above the screening trigger value of 4.5.

An OECD TG 305 study (aqueous exposure; reliable without restriction) with rainbow trout (*Oncorhynchus mykiss*) performed on UV-326 indicates a high bioaccumulation potential with a lipid-normalised growth corrected kinetic bioconcentration factor (BCF_{kgL}) value in the range of 7093—14225 L/kg (whole fish BCF back calculated from edible and non-edible portions and based on total radioactive residues of the test substance). This study is given a high weight and its results are used to conclude that UV-326 has B/vB properties (BCF>5000 L/kg) in accordance with REACH Annex XIII. Monitoring data tend to confirm this prediction as UV-326 has been found in human breast milk and in biota including in top predators such as the polar bears which are listed as vulnerable to extinction, according to the International Union for Conservation of Nature (IUCN) Red List. Based on the weight of evidence of the data available, it is concluded that UV-326 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.1.2 and 1.2.2, of the REACH Regulation.

Conclusion

In conclusion, UV-326 is identified as vPvB substance according to Art. 57(e) of REACH by comparing all relevant and available information listed in Annex XIII of REACH with the criteria set out in the same Annex, in a weight-of-evidence determination.

Registration dossiers submitted for the substance: Yes

Justification

1 Identity of the substances and physical and chemical properties

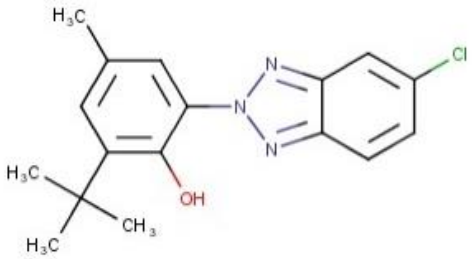
1.1 Name and other identifiers of the substances

Table 1: Substance identity for UV-326

(Bumetrizole)

EC number:	223-445-4
EC name:	Bumetrizole
CAS number (in the EC inventory):	3896-11-5
CAS number:	3896-11-5
IUPAC name:	2-tert-butyl-6-(5-chloro-2H-benzotriazol-2-yl)-4-methylphenol
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	$C_{17}H_{18}ClN_3O$
Molecular weight:	315.8 g/mol
Synonyms:	2-(2'-Hydroxy-3'-t-butyl-5'-methylphenyl)-5-chlorobenzotriazole 2-(2-Hydroxy-3-*tert*-butyl-5-methylphenyl)-5-chloro-2*H*-benzotriazole 2-(3'-*tert*-butyl-2'-hydroxy-5'-methylphenyl)-5-chlorobenzotriazole 2-(5-Chloro-2-benzotriazolyl)-6-*tert*-butyl-p-cresol 2-(5-Chloro-2*H*-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methylphenol 2-*tert*-butyl-6-(5-chloro-2*H*-1,2,3-benzotriazol-2-yl)-4-methylphenol 2-*tert*-Butyl-6-(5-chloro-2*H*-benzotriazol-2-yl)-p-cresol 2-*tert*-Butyl-6-(5-chloro-2*H*-benzotriazol-2-yl)-4-methylphenol 2-*tert*-butyl-6-(5-chlorobenzotriazol-2-yl)-4-methylphenol Phenol, 2-(5-chloro-2*H*-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methyl- UV-326

Structural formula:



1.2 Composition of the substance

Name: Bumetrizole (UV-326)

Substance type: mono-constituent

Table 2: Constituents other than impurities/additives (for UV-326)

Constituents	Typical concentration	Concentration range	Remarks
2-(2'-hydroxy-3'-tert-butyl-5'-methylphenyl)-5-chloro benzotriazole (EC: 223-445-4)	≤100 %		

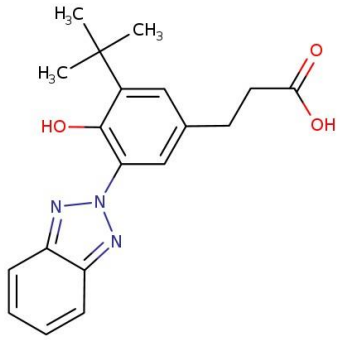
1.3 Identity and composition of structurally related substance M1 (read-across approach)

Table 3: Structurally related substance identity of M1

List [1]number:	630-348-4
List name:	3-[3-(2*H*-benzotriazol-2-yl)-5-*tert*-butyl-4-hydroxyphenyl]propanoic acid
SMILES:	CC(C)(C)c1cc(CCC(O)=O)cc(n2nc3ccccc3n2)c1O
CAS number (in the EC inventory):	84268-36-0
CAS number:	84268-36-0
IUPAC name:	3-[3-(2*H*-benzotriazol-2-yl)-4-hydroxy-5-(2-methyl-2-propanyl)phenyl]propanoic acid
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	$C_{19}H_{21}N_3O_3$
Molecular weight range:	339.39 g/mol
Synonyms:	*3-(2H-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid* *3-[3-(2H-1,2,3-benzotriazol-2-yl)-5-tert-butyl-4-hydroxyphenyl]propanoic acid* *3-[3-(2H-Benzotriazol-2-yl)-5-tert-butyl-4-hydroxyphenyl]propionic acid* *M1*

Structural formula:

[1] Explanation on the role of List numbers is provided in the ECHA website at: https://echa.europa.eu/information-on-chemicals/registered-substances/information



Substance type: mono-constituent

Table 4: Constituents of structurally related substance M1

Constituents	Typical concentration	Concentration range	Remarks
3-[3-(2H-1,2,3-benzotriazol-2-yl)-5-tert-butyl-4-hydroxyphenyl]propanoic acid (EC: 630-348-4)	≤100 %		

1.4 Physicochemical properties

Table 5: Overview of physicochemical properties of UV-326 (2-(2'-hydroxy-3'-*tert*-butyl-5'-methylphenyl)-5-chloro benzotriazole)[2]

Property	Description of key information	Value [Unit]	Reference/source of information
Physical state at 20°C and 101.3 kPa	*visual inspection*	*solid* *slightly yellow powder*	*ECHA dissemination page*
Melting/freezing point	*Differential Scanning Calorimetry (DSC) method*	*139.7 °C* *(137 – 141 °C by Capillary method)*	*ECHA dissemination page*
Boiling point	*TGA - dynamic screening method*	*>225 °C (decomposition; w/o boiling)*	*ECHA dissemination page*
Vapour pressure	*The calculation was based on Modified Grain Method using recommended MPBPVP (v1.43) module of software EPI Suite v.4.00*	*0.00000075 Pa (at 20 °C)*	*ECHA dissemination page*
Density	*Internal analytical method*	*1320 kg/m³ (at 20 °C)*	*ECHA dissemination page*
Water solubility	*OECD Guideline 105 (Water Solubility)* *Column elution method (HPLC)*	*4 µg/L (at 20 °C; pH 6.3)*	*ECHA dissemination page*
Partition coefficient n-octanol/water (log value)	*OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method)*	*5.4 – 6.4 (at 23 °C)* *≥6.5 (at 23 °C, pH 6.4)*	*ECHA dissemination page*
	Estimated using COSMOtherm	*6.7*	*COSMOconf[3]* *COSMOtherm[4]*
	Experimental	*7.38*	*Do et al. (2022)*

[2] https://echa.europa.eu/de/substance-information/-/substanceinfo/100.021.315
Access date ECHA dissemination page for all information on 08.03.2023
[3] COSMOconf conformer generation performed using the BP-TZVP-COSMO+GAS template; BIOVIA COSMOconf, Release 2021; Dassault Systèmes. http://www.3ds.com
[4] COSMOtherm property estimation performed using the BP_TZVP_21-parameterisation; BIOVIA COSMOtherm, Release 2021; Dassault Systèmes. http://www.3ds.com;

Dissociation constant	*The calculation was using the recommended software program SPARC v4.5*	*pKa = 10 (at 25 °C)*	*ECHA dissemination page*
	Calculated with Chemicalize	*Strongest acidic pKa = 10.18 (at 25°C)*	*Chemicalize*[5]
	ACD Percepta prediction	*pKa = 10.2 (at pH 9, no temperature available)*	*ACD/Labs*[6]
For UV-326 ionisation can only occur at the hydroxyl group, as this is the only functional group that could act as proton acceptor/donor. However, this group is stabilized by the aromatic system as well as via hydrogen bonds by the nitrogen atoms. Thus, dissociation is very unlikely to occur at environmentally relevant pH values of 4 – 9. ACD Percepta predicts a pKa of 10.2 and that at pH 9 6 % of UV-326 is present in ionised form (hydroxy group negatively charged). At lower pH values the share of the ionised form is further reduced leading to an even higher share of the non-ionised form. In the relevant pH range (4 – 9) the non-ionised form is dominant.			

Table 6: Overview of physicochemical properties of structurally related substance M1

Property	Description of key information	Value [Unit]	Reference/source of information
Physical state at 20°C and 101.3 kPa	*Visual inspection*	*Solid* *Light yellow powder*	*ECHA dissemination page*
Melting/freezing point	*DSC according to OECD Guideline 102*	*195 °C*	*ECHA dissemination page*
Boiling point	*DSC according to OECD Guideline 103*	*no boiling observed up to 400 °C*	*ECHA dissemination page*

[5] 27.10. 2022, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)
[6] ACD Percepta. ACD/Labs release 2019.2.1 (2019), Advanced Chemistry Development, Inc.

Vapour pressure	*No method given*	*2.933 10^{-10} Pa (at 25 °C)*	*ECHA dissemination page*
Density	*OECD Guideline 109 (pycnometer)*	*785 kg/m³ (at 20 °C)*	*ECHA dissemination page*
Water solubility	*OECD Guideline 105 (flask method)*	*<0.001 g/L (at 20 °C, pH 7.1)*	*ECHA dissemination page*
Partition coefficient n-octanol/water (log value)	*OECD Guideline 107 (shake flask method)*	*≥ 2.75 (at 25 °C, pH 6.9)*	*ECHA dissemination page*
	Estimated using COSMOtherm via pKa from M1-Anion	*3.32 (no temperature available)*	*COSMOconf[7] COSMOtherm[8]*
Dissociation constant	*Calculated with Chemicalize*	*Strongest acidic pKa = 4.25 (at 25°C)*	*Chemicalize[9]*
The substance M1 comprises two functional groups that could act as proton acceptor/donor. The hydroxyl group is stabilized via the aromatic system and protected via hydrogen bonds by the nitrogen atoms. Thus, dissociation is very unlikely to occur. The carboxyl group instead will dissociate in the environmental relevant pH range of 4 – 9. Due to the pKa of 4.25 and the chemical structure it is expected that the substance will be mainly present in its ionised form at pH 4 – 9.			

[7] COSMOconf COSMOtherm C_30_1601.ctd Dassault Systèmes. http://www.3ds.com;
[8] COSMOtherm COSMOtherm C_30_1601.ctd Dassault Systèmes. http://www.3ds.com;
[9] 19.08. 2023, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)

2 Harmonised classification and labelling

2-(2'-hydroxy -3' -*tert*-butyl-5'-methylphenyl)-5-chloro benzotriazole (UV-326 (EC: 223-445-4; CAS 3896-11-5) has no harmonised classification in part 3 of Annex VI to the CLP Regulation.

The following hazard classes are contained in self-classifications notified to the CLP inventory[10]:

- Aquatic Chronic 4 (H413)
- Aquatic Chronic 3 (H412)
- Skin Irrit. 2 (H315)
- Eye Irrit. 2 (H319)
- STOT SE 3 (H335)
- Acute Tox. 4 (H312))
- Aquatic Acute 1 (H400)
- Aquatic Chronic 2 (H411)

[10] https://echa.europa.eu/de/information-on-chemicals/cl-inventory-database/-/discli/details/44804

3 Environmental fate properties

Considerations on chemical structure and properties and justification for read-across

UV-326 is part of a group of phenolic benzotriazoles which are also called UV-benzotriazoles. These substances share the 2-(2-hydroxyphenyl)-2*H*-benzotriazole moiety as a common structural feature. The intramolecular hydrogen bond between the hydroxy group and the nitrogen of the benzotriazole ring is essential for their function as UV absorbers (see Figure 1).

Information on some structurally related phenolic benzotriazoles is used in this dossier for a read-across or as supporting evidence. Thus, a brief general description of the group is given along with a more detailed discussion of the substance M1 that is relevant for the assessment. A data matrix is given in the appendix to support the read-across.

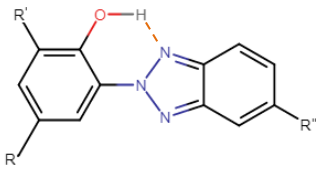


Figure 1: Structures of phenolic benzotriazoles

(R = alkyl, alkylphenyl; R‵ = H, alkyl, alkylphenyl; R‵‵ = H, Cl).

Due to the structural similarity of the substances, similar properties are expected which vary depending on the different substituents. In combination with the substituents described in Figure 1, the 2-(2-hydroxyphenyl)-2*H*-benzotriazole moiety common to all substances is associated with high stability and lipophilicity. Accordingly, water solubility is rather low and adsorption potential is expected to be high. This is confirmed by the available data (see Annex I and ECHA 2014a, 2014b, 2015a, 2015b). The substances are not volatile and volatilisation is not expected to impact degradation (see Annex I and ECHA 2014a, 2014b, 2015a, 2015b, ECHA 2022).

Generally, the alkyl substituents are considered to increase lipophilicity and to reduce water solubility – the larger the substituents, the more lipophilic the molecule. Furthermore, substituents in ortho position to the hydroxy group provide a steric stabilisation to the intramolecular hydrogen bond. Finally, the absence of substituents at the phenyl moiety might theoretically enable enzymatic attacks at the respective molecular sites.

The very high persistence and very high bioaccumulation of the structurally related substances UV-320, UV-328, UV-327 and UV-350 has previously been confirmed by their identification as SVHC substances due to their vPvB properties.

UV-326 bears a high similarity to these substances, especially to UV-327: there are alkyl substituents in ortho and para position to the hydroxy group. Both UV-326 and UV-327 have a chlorine substituent in the benzotriazole moiety. Hence, UV-326 is expected to have comparable physico-chemical and degradation properties to UV-327. This expectation is supported by the available data, i.e. QSAR predictions, ready biodegradation tests, a water sediment study, findings in sediment cores and a soil dissipation study (see Annex I and ECHA 2015a). While a read-across from UV-327 to UV-326 could be justified based on structural similarity, the data set for both substances is so similar that no new lines of evidence are expected from such a read-across.

Another structurally related substance is M1 (EC 630-348-4), a metabolite of UV-384 (EC 407-000-3). Information on M1 has been used for read-across in the persistence assessments of UV-320, UV-328, UV-327, and UV-350 in order to conclude on their vP properties and is provided in

this dossier for read-across as well.

M1 differs from UV-326 regarding the substituent in para position to the hydroxy group, which is a carboxyethyl group for M1 and a methyl group for UV-326, respectively. Furthermore, UV-326 has a chlorine substituent in the benzotriazole moiety and M1 has not. These differences – carboxyethyl group vs. alkyl group, chlorine substituent vs. no chlorine substituent are comparable to the differences between M1 and UV-327.

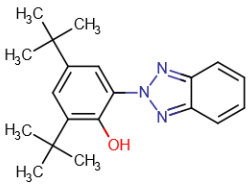
The carboxyethyl group is a characteristic structural feature that differentiates M1 from the group of phenolic benzotriazoles described in figure 1. As described above in section 1.4 , the carboxyethyl group has an impact on dissociation. M1 is expected to be present in the dissociated form under environmentally relevant pH values. Therefore, M1 is expected to have a higher water solubility and a lower octanol water partition coefficient than UV-326. However, as adsorption of M1 might be enhanced by ionic interactions, it is expected to have a high adsorption potential as well. These expectations are supported by the available physico-chemical data (see Annex I). Thus, the bioavailability of M1 is expected to be similar as compared to UV-326. The carbonic acid group might also enhance degradability of the respective side chain (Gao et al. 2010, EAWAG 2023).

In summary, M1 is structurally similar to UV-326. Based on mechanistic considerations and biodegradation estimations[11] it is expected that M1's susceptibility to degradation is similar to or higher than that of UV-326 (DegT50(M1) ≤ DegT50(UV-326)).

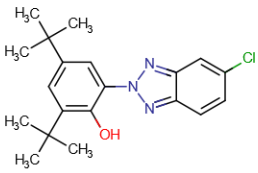
The impact of impurities is not considered relevant for a read-across from M1 to UV-326: The data used for read-across refer to detection of the substance as a major metabolite in a simulation test (M1).

As outlined above, the available data support the proposed similarity of UV-326 and M1 in degradation properties (see Annex I).

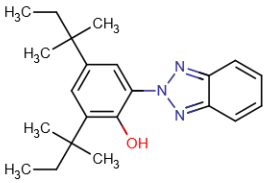
[11] All BIOWIN models predict a better biodegradability for M1 than for UV-326.
The CATALOGIC model 301C v12.17 predicts UV-326 and M1 to be not readily biodegradable. The extrapolated primary half-life values predicted with this model are 9 months 26 days for UV-326 and 1 year 3 months 26 days for M1.
As discussed further below, CATALOGIC 301C v12.17 is preferred because its training set contains the most phenolic benzotriazoles. The automatic applicability domain check shows that this model is also the best for M1 while it is still denoted "out of domain"due to 5% unknown fragments.



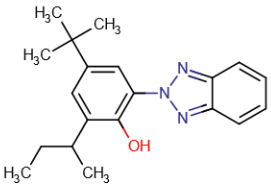
UV-320



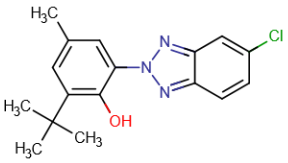
UV-327



UV-328

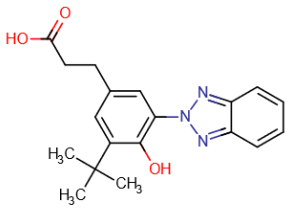


UV-350



UV-326

Figure 2: Structures of UV-326 and the known SVHC substances UV-320, UV-328, UV-327 and UV-350 identified as vP.



M1

Figure 3: Structure of M1.

3.1 Degradation

A weight-of-evidence approach is applied for the assessment of persistence. The "Weight of Evidence/Uncertainty Analysis Template[12]" is applied to structure the data.

3.1.1 Problem Formulation

A weight of evidence determination according to the provisions of Annex XIII of REACH is used to assess if the substance meets the criteria for P/vP.

3.1.2 Documentation of search strategy & documentation/reporting of evidence

Information/evidence used in the approach includes:

- Experimental studies from ECHA dissemination site
- (Q)SAR results
- Published Literature
- Research Project
- Information on structurally related substances

[12] https://echa.europa.eu/documents/10162/17169198/template_for_weight_of_evidence_en.docx/eb183c2e-c360-cbce-7a58-ad2d1270e5bd

3.1.3 Collection and documentation of all information

In addition to the information from the registration dossiers, further studies were used for persistence assessment. These are documented in the Reference List.

The assessment includes field studies in sediment and soil. Various further monitoring data are available: UV-326 has been detected in freshwater and marine sediments (for example Wick *et al.*, 2016a and 2016b[13]; Kameda *et al.*, 2011; Nakata *et al.*, 2009; Apel *et al.*, 2018, Schlabach *et al.*, 2019), in surface water (for example Tashiro and Kameda, 2013; Khare *et al.*, 2023; Schlabach *et al.*, 2019) and in soil (Heimstad *et al.*, 2021).

According to the PBT guidance, monitoring data may be indicative of persistence, but the impact of factors other than persistence needs to be taken into account (ECHA, 2017). In many cases, it is not clear to which extent the detection of a substance is due to slow degradation, and to which extent due to exposure. Actually, both factors are expected to have an impact for UV-326.

The available data from sediment cores (cf. section 3.1.4.2.4) and soil dissipation studies (cf. section 3.1.4.3.1) contain information on contamination after a certain time span. Thus, their informative value for persistence assessment is greater than that of the other monitoring studies. The other available studies are not considered further in the assessment because they contain a high degree of uncertainty and they are not considered to have a significant impact on the conclusion.

3.1.4 Assessment of quality of individual evidence

3.1.4.1 Abiotic Degradation

Table 7: Data on abiotic degradation for UV-326

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
HYDROWIN[14]	The program reports that the substances do not belong to the substance classes for which hydrolysis is predicted. This result indicates the absence of "classical" hydrolysable groups, but does not prove that the substance is hydrolytically stable.	Phenolic benzotriazoles are outside the application domain; the program reports that they do not belong to the substance classes for which hydrolysis is predicted. Klimisch score 3	Adequacy to be considered within integration of evidence
CATALOGIC Abiotic[15]	Screening information on aerobic abiotic degradation under OECD TG 301 C testing conditions. This model was calibrated on experimental data on parent chemicals and their transformation products. The model predicts abiotic degradation under the conditions of a ready biodegradability test,	CATALOGIC includes an automatic check of application domain.[17] The domain check accounts for molecular fragments and is stricter as compared to HYDROWIN. UV-326 is in the parameter range of the model. However, it is out of the applicability domain due to > 50% unknown structural	Adequacy to be considered within integration of evidence

[13] Wick et al. 2016a and 2016b contain both monitoring data and water sediment studies. While this section refers to the monitoring data, the water sediment studies are discussed below.
[14] 2017 U.S. Environmental Protection Agency. HYDROWIN v2.00 in EPISUITE v4.11. Result for all structures: The chemical structure does not contain typical functional groups that are susceptible to hydrolysis.
[15] OASIS CATALOGIC v.5.15.2.14. http://oasis-lmc.org/products/software/catalogic.aspx (November 2022); CATALOGIC Abiotic 301C v.01.08
[17] Default setting tolerates a certain percentage of unknown fragments; adjusted setting: No unknown fragments accepted.

	including hydrolysis as a major abiotic transformation pathway.[16]	fragments. Klimisch score 3	

No experimental data on hydrolysis are available. The HYDROWIN and CATALOGIC results are outside the applicability domain and thus considered as not reliable (Klimisch score 3).

The structure of UV-326 does not contain functional groups that are susceptible to hydrolysis, a finding that is supported by HYDROWIN results. The CATALOGIC Abiotic 301 C model predicts no abiotic transformation for UV-326 under the testing conditions of OECD TG 301 C. Thus, it is assumed that the substance is hydrolytically stable.

No data on photolysis or oxidation are available in the registration dossier for UV-326.

3.1.4.2 Biodegradation in aqueous media or aqueous environment

3.1.4.2.1 Estimated data

Table 8: Estimated data on biodegradation for UV-326

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
BIOWIN[18]	Screening information on biodegradation. BIOWIN models 1,2,5,6 were calibrated based on screening tests for ready biodegradability, i.e., these models predict respective test results. BIOWIN 3 and 4 are based on results of an expert survey and predict the semi-quantitative timeframe for Ultimate and Primary Biodegradation, respectively. As these models were not calibrated to experimental data, but to an expert survey, BIOWIN 3 and 4 can be regarded to predict the result of a respective expert judgement. [19]	The BIOWIN user guide recommends to assess the applicability domain using the Molecular Weight range and the fragment count, i.e., to check whether the occurrence of a given fragment in the predicted compound exceeds the maximum occurrence of that fragment per molecule in the training set. UV-326 is in the Molecular Weight range of the model's training sets. For UV-326, the molecular fragments used for calculation do not exceed the maximum number of such fragments per molecule observed in the training set. A search for structurally related structures in the available information on the training set was carried out: The training set for BIOWIN 1 and 2 does not contain benzotriazoles. BIOWIN 3 and 4 were trained on the structurally related substance 2-(2*H*-Benzotriazol-2-yl)-phenol[20] which enhances their applicability to the target substance. The predicted BIOWIN 3 and 4 values for this substance are in good agreement with the survey average. The training set (old) for BIOWIN 5 and 6 does not contain benzotriazoles, but 1*H*-Benzotriazole is in the validation set[21] and is correctly predicted as not readily biodegradable.	Adequacy to be considered within integration of evidence

[16] http://oasis-lmc.org/products/models/environmental-fate-and-ecotoxicity.aspx (November 2022)
[18] 2017 U.S. Environmental Protection Agency. BIOWIN v4.11 in EPISUITE v4.11
[19] 2017 U.S. Environmental Protection Agency. BIOWIN v4.11 in EPISUITE v4.11. User Guide.
[20] Substance no. 88, 2-(2H-Benzotriazol-2-yl)-phenol
[21] Substance no. 95147, 1H-Benzotriazole

CATALOGIC[22]	Screening information on biodegradation. The applied CATALOGIC biodegradation models were calibrated on data from OECD 301 test results and on information on biodegradation pathways. These models predict biodegradation under the conditions of a ready biodegradability test.[23]	CATALOGIC includes automatic check of application domain.[24] The domain check accounts for molecular fragments and is stricter as compared to BIOWIN. UV-326 is in the parameter range of the models. The structural domain check is stricter than that recommended for BIOWIN. Only the result of the CATALOGIC 301C v12.17 model for UV-326 is considered in domain. All other predictions for UV-326 are considered out of domain. It is noted that applying such a domain check to models like BIOWIN would result in all or almost all predictions being out of domain as well.	Adequacy to be considered within integration of evidence

3.1.4.2.1.1 BIOWIN

The BIOWIN software, as described in Table 8, yields the following results:

Table 9: BIOWIN results

Name	BIOWIN1 (Linear Model)	BIOWIN2 (Non-Linear Model)	BIOWIN3 ultimate	BIOWIN4 primary	BIOWIN5 (Linear MITI Model)	BIOWIN6 (Non-Linear MITI Model)	R11 screening
UV-326	0.4013	0.0235	2.0641	3.0445	0.0650	0.0086	fulfilled

For the BIOWIN models 1, 2, 5 and 6 a result greater than or equal to 0.5 indicates that the substance is predicted to be readily biodegradable. A result below 0.5 indicates that the substance is not readily biodegradable. The BIOWIN user guide recommends to assess the applicability domain using the Molecular Weight range and the fragment count, i.e., to check whether the occurrence of a given fragment in the predicted compound exceeds the maximum occurrence of that fragment per molecule in the training set. UV-326 is in the Molecular Weight range of the model's training sets. For UV-326, the molecular fragments used for calculation do not exceed the maximum number of such fragments per molecule observed in the training set. While none of these models were trained on benzotriazoles[25], the validation set of BIOWIN 5 and 6 at least contained the structurally related 1*H*-Benzotriazole, which was predicted correctly as not readily biodegradable. The updated training and validation sets contain UV-320 (training set) and UV-P, UV-326 and 1H-Benzotriazole (all validation set). Therefore, BIOWIN 5 and 6 are considered more reliable than BIOWIN 1 and 2.

UV-326 is predicted to be not readily biodegradable by BIOWIN 1, 2, 5 and 6.

BIOWIN models 3 and 4 indicate the timeframe for ultimate and primary biodegradation, respectively. BIOWIN 3 and 4 were trained on the structurally related substance 2-(2*H*-Benzotriazol-2-yl)-phenol which enhances their applicability to the target substance. Predicted biodegradation timeframes for UV-326 are "Months" (ultimate) and "Weeks" (primary).

[22] OASIS CATALOGIC v.5.15.2.14. http://oasis-lmc.org/products/software/catalogic.aspx (November 2022); CATABOL 301B v.02.07; CATABOL 301C v.02.08; CATALOGIC 301C v.12.17; CATALOGIC Kinetic 301B v.02.11; CATALOGIC Kinetic 301F v.15.18

[23] http://oasis-lmc.org/products/models/environmental-fate-and-ecotoxicity.aspx (November 2022)

[24] Default setting tolerates a certain percentage of unknown fragments; adjusted setting: No unknown fragments accepted.

[25] Additional training set data from 2017 update to BIOWIN 5 and 6 were not available. If these contained benzotriazoles, they might improve the applicability of the model. In summary, this would not change the finding that BIOWIN 5 and 6 are assumed to be more reliable for these substances than BIOWIN 1 and 2.

According to REACH Chapter R.11 (ECHA, 2017[26]), a substance is considered as potentially P or vP if the estimated probability value for Biowin 2 or 6 is below 0.5, and the estimated probability value for Biowin 3 is below 2.25 (to 2.75).

Based on the screening criteria from the guidance, UV-326 is considered to be potentially P or vP.

[26] ECHA 2017. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT/vPvB assessment. Version 3.0.
https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf/a8cce23f-a65a-46d2-ac68-92fee1f9e54f (accessed November 2022)

3.1.4.2.1.2 CATALOGIC

The CATALOGIC software includes an automatic applicability domain check. The following results were obtained:

Table 10: Results of CATALOGIC applicability domain check

Name	CATALOGIC 301C v12.17	CATABOL 301C v02.08	CATABOL 301B v02.07	CATALOGIC Kinetic 301B v02.11	CATALOGIC Kinetic 301F v15.18
UV-326	In domain, belongs to training set	Out of Domain (5.88% unknown fragments)	Out of Domain (64.71% unknown fragments)	Out of Domain (76.47% unknown fragments, out of mechanistic domain)	Out of Domain (64.71% unknown fragments)

The training set of CATALOGIC 301 C v12.17 contains UV-326 and the structurally related phenolic benzotriazoles UV-P, UV-327, UV-328, UV-350 and UV-320.[27] The training set of CATABOL 301 C v02.08 contains UV-327. In summary, CATALOGIC 301 C v12.17 is considered the preferred model, as its training set contains structurally related compounds and the substance is in the applicability domain.

The substance is predicted not readily biodegradable. The CATALOGIC 301 C v12.17 model estimates 0% ultimate biodegradation in 28 days under OECD 301 C conditions.

The model additionally predicts ultimate and primary half-life values that are estimated based on extrapolated data from OECD 301 tests:

Table 11: CATALOGIC results for extrapolated ultimate and primary half-life values (expressed as days (d), months (m) and years (y))

Name	CATALOGIC 301C v12.17	
	Primary Half-life	Ultimate Half-life
UV-326	9m 26d	more than 10 y

Degradation kinetics observed in OECD 301 tests cannot be extrapolated to relevant conditions of REACH Annex XIII. Therefore, the respective results should be treated with caution. However, they may give an indication of the expected degradation kinetics under prolonged / extrapolated OECD 301 testing conditions.

CATALOGIC 301 C v12.17 predicts primary half-life values in the range of months and ultimate half-life values in the range of years for UV-326 thus indicating the substance screens as potentially P/vP.

[27] The training set results for UV-P, UV-327, UV-328, UV-350 and UV-320 range from 0% to 8% ultimate biodegradation in 28 days. The respective predicted ultimate biodegradation in 28 days ranges from 0% to 1%.

3.1.4.2.2 Screening tests

Table 12: Screening tests on ready biodegradability

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
Biodegradation Screening test OECD TG 301B (Testing Laboratory 2007) UV-326	Yes, according to test guideline protocol covering parameters required for assessment.	Klimisch score 2	Adequate study for biodegradation in water
Biodegradation Screening test OECD TG 301C (Testing Laboratory 1996) UV-326	Yes, according to test guideline protocol covering parameters required for assessment.	Klimisch score 1	Adequate study for biodegradation in water
Biodegradation Screening test OECD TG 301B (Testing Laboratory 1988) UV-326	Yes, according to test guideline protocol covering parameters required for assessment.	Klimisch score 2	Adequate study for biodegradation in water

Relevant and reliable screening tests on ready biodegradability are available for UV-326. The highest degradation observed in the OECD 301 screening tests was ≤20% in one OECD 301B study on UV-326. No biodegradation was observed in the other OECD 301 tests.

Three screening tests on ready biodegradability are available for **UV-326**:

- The registration dossier contains an OECD 301 B study from 2007 that is considered as key study by the registrant. For the applied testing concentration of 16 mg/L, the observed CO_2 evolution after 28 days was ≥10% and ≤20%.
- The OECD 301 C study from the registration dossier is also considered as key study by the registrant. The applied test concentration was 100 mg/L and the test duration 28 days. The degree of degradation was determined by BOD measurement and test material analysis, both yielding 0% of degradation.
- Another OECD 301 B study is available in the registration dossier. This study was conducted in 1988 and is considered as supporting study by the registrant. For the applied testing concentrations of 10 mg/L and 20 mg/L, 10% and 2% CO_2 evolution were observed after 28 days, respectively.

3.1.4.2.3 Simulation tests

Table 13: Water sediment simulation tests

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
Water-sediment simulation study (non-GLP study) (Wick et al 2016a, Wick et al 2016b) UV-326	Yes, according to test guideline protocol covering parameters required for assessment.	Klimisch score 2	Adequate study for biodegradation in water sediment systems
Aquifer simulation study (Liu et al. 2013) UV-326	Relevant with restriction: Study design specifically targeted on aquifer systems, but study contains information on dissipation in a system of water and aquifer	Klimisch score 2	Adequate study for biodegradation in aquifer systems

	sediment. Methodology described, covering most parameters required for assessment		
OECD TG 308 Simulation study on UV-384 (EC 407-000-3) and its metabolite M1 (ECHA 2014a)	Yes, according to test guideline protocol covering parameters required for assessment.	Klimisch score 2	Adequate study for biodegradation of a structurally related substance (M1) in water sediment systems.

3.1.4.2.3.1 Study on UV-benzotriazoles in a river water-sediment system (Wick et al. 2016a, Wick et al 2016b)

Wick *et al.* (2016a, 2016b) investigated the biodegradation of UV-326 and other phenolic benzotriazoles[28] in an aerobic water-sediment study. This non-GLP study shows some variations to the OECD TG 308:

- Only one sediment was used with a relatively high TOC of 4.22% (fine texture, as required);
- the sediment was freshly collected at a site where previous contamination with organic chemicals may be expected[29], resulting in possible pre-adaptation of micro-organisms;
- volatiles were not collected.

Besides that, test conditions were in accordance with OECD TG 308: equilibration time 4 weeks; test temperature 20 °C; a pH range of 7.8 to 8.4 and O_2 concentrations of 8.8 to 9.1 mg/L. No information on redox potential is available. The test was conducted in 250 mL amber glass bottles that were filled with sediment and surface water at a ratio of 1:4 (w/w). 2 µg radioactively non-labelled test substance was dissolved in 100 µL methanol and spiked into the water phase. The initial test concentration for each individual benzotriazole was 10 µg/L in the supernatant, which was applied as a mixture.
Triplicate sampling was conducted at 0 (30 min), 2, 4, 8, 16, 25, 50 and 100 days after spiking; test duration was 100 days. Extraction of the freeze-dried sediment samples was done by pressurised liquid extraction (PLE) followed by silica clean-up. Analysis of the test substances was accomplished by LC-MS/MS measurements. An external standard calibration with 14 calibration points ranging from 0 to 100 µg/L and a linear fitting were used for quantification.

A parallel test with the reference substance Lenacil showed degradation of up to 50% on day 100 in the total system, thus demonstrating the microbial viability of the test system. Results for this test are presented in Figure 4.

For all analysed phenolic-benzotriazoles, a gap in the mass balance was observed at the beginning of the incubation period (until day 16), before the sorption equilibrium between water and sediment was reached (see Figure 4). This is probably due to an underdetermination of the dissolved concentrations due to a strong sorption of the substances on the vessel walls. In the subsequent period between day 16 and day 100, however, the recoveries were mostly within the range of the OECD Guideline 308 target (70-110%). From day 16 onwards, recoveries were relatively constant and the standard deviations were mostly below 20%.

The results confirmed the high sorption affinity of the phenolic-benzotriazoles. After 16 days, no substance could be detected in the water phase. Taking into account the quantification limits for the water phase[30,] it was found that >99.5% of the amount of UV-326 were sorbed

[28] This study also includes results for UV-327 and UV-350 that are discussed in the respective SVHC dossiers for these substances (ECHA 2015a, ECHA 2015b).
Different phenolic benzotriazoles were tested together in common test vessels. However, the impact of co-exposure to other phenolic benzotriazoles is expected to be negligible because:

- similar susceptibility to degradation is expected (see discussion on structure and properties above in section 3)
- no degradation was observed, i.e. enhanced biodegradation by co-metabolism was not significant under testing conditions
- no toxicity to microorganisms is expected based on the available data for the tested substances.

[29] River Rhine, Germany (Koblenz, harbor, river km 591.4)
[30] Limit of quantification in water (LOQ_{water}):
LOQ_{water} = 0.04 µg/L for UV-326, UV-329, UV-328 and UV-327 and UV-350
LOQ_{water} = 0.01 µg/L for UV-928 and UV-234

on the sediment. Due to the intensive extraction method, which was specifically designed to recover as much of the non-radioactive test substance as possible, there were practically no "non-extractable residues" (NER). No significant decrease in total concentration was observed for any of the phenolic benzotriazoles investigated during the 100 d incubation period. Therefore, no degradation kinetics could be modelled – any rate constants derived would probably not significantly differ from zero. The calculation of a half-life from such modelled rate constants would probably not be meaningful.

Consequently, the phenolic benzotriazoles were persistent in the experiment and the half-life was significantly higher than the observation period of 100 d. At an environmentally relevant temperature of 12 °C this corresponded to a half-life significantly larger than 212 days for UV-326 .

The impact of the deviations from OECD TG 308 is not considered detrimental in this test because:

- the chosen sediment was appropriate for the test and as no biodegradation was observed, it can be considered as worst case;
- the possible pre-adaptation of micro-organisms did not lead to the observation of biodegradation;
- volatiles were not collected but recovery was sufficient and neither degradation nor volatilisation were observed.

This study is considered as reliable with restrictions.

In conclusion, UV-326 rapidly and nearly completely adsorbs to sediment in a water/sediment system and hardly degrades over a period of 100 days (DegT50, sed. >>100 d).

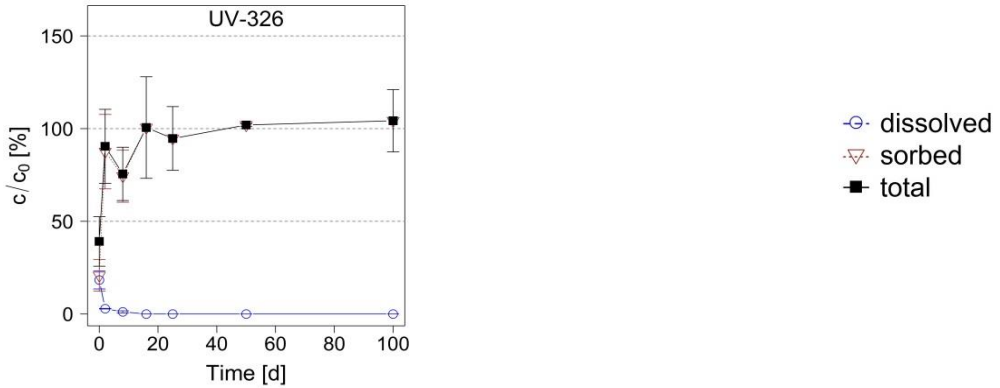


Figure 4: Average relative concentrations [% of initial concentration c0] of UV-326 in sediment-water systems incubated for 100 d at 20 ± 1 °C in a climate cabinet (n=3). The error bars represent the standard deviation (taken from Wick et al., 2016a, supporting data).

3.1.4.2.3.2 Study on UV-326 in aquifers

Dissipation of a mixture of different UV-filters in an aquifer system was studied by Liu et al., 2013. Among the test substances there are UV-326 and another phenolic benzotriazole (UV-329); but also UV filters that are significantly more susceptible to biodegradation than

phenolic benzotriazoles, e.g. benzophenone-3.[31] All tested UV-filters were present in each treatment and the authors assume that interaction effects on degradation are negligible; however, co-metabolism could potentially have occurred. The study was conducted using in different treatments, one of which was aerobic. The other treatments referred to specific anaerobic conditions that are considered to have a lower relevance for persistence assessment. The aerobic treatment is reported in more detail as it is considered the most relevant part of the study for persistence assessment. The study appears to be well-conducted, but it simulates the fate of UV filters in aquifers rather than in ponds, rivers or in the sea. Hence, there are some characteristic differences to OECD TG 308:

- Only one sediment was tested (low TOC of 0.4%[32], coarse texture)
- Material for sediment was taken from the aquifer 5 m below the ground surface
- Groundwater sampled from a well nearby with a very low level of dissolved oxygen (0.4 mg/L)
- Smaller test systems & deviating water sediment ratio (5 g aquifer + 5 mL water)[33]
- The test system was not checked for transformation products.

As no information on equilibration time is available, it is uncertain whether and how equilibration was conducted. The aerobic treatment was conducted in a laminar flow chamber by opening the caps three times a day; however, no information on the level of dissolved oxygen during the test is available.

Anaerobic treatments were handled under exclusion of oxygen. These included an anaerobic control (i.e., anaerobic treatment without addition of reducing agents), and three reducing treatments. The reducing treatments were prepared by the addition of Na_2S (1 mM) and sodium lactate (10 mM). Either $NaNO_3$ (20 mM), Na_2SO_4 (20 mM), or Fe(III) citrate (20 mM) were added to generate nitrate-reducing, sulfate reducing or Fe(III) reducing conditions, respectively.

The incubation temperature was 20 °C and the initial concentration of each compound was given as 1 mg/L. A stock solution was prepared from the radioactively non-labelled test substances and methanol (concentration of each test substance 100 mg/L); this solution was used to apply the tests substances in the reaction tubes. The description indicates that the substances were pipetted into each test vessel with an applied concentration of 1 µg/g per substance in the aquifer sediment (50 µL stock solution). Triplicate sampling was conducted for each treatment at days 0, 7, 14, 21, 28, 35, 49, 63, and 77; test duration was 77 days. Extraction of the freeze-dried sediment samples was done by pressurised liquid extraction (PLE). Analysis of the test substances was accomplished by GC-MS/MS measurements. Based on sterile groundwater and aquifer material systems a recovery of 94% was determined for UV-326. Total numbers of culturable bacteria in each treatment were monitored on each sampling.

Sterile controls (aerobic and anaerobic) were autoclaved at 120 °C for 20 minutes on three consecutive days followed by treatment with sodium azide. The authors report that all tested UV-filters did not dissipate under sterile conditions.

The observed dissipation of UV-326 was faster in the aerobic treatments than in the anaerobic treatments.[34] For UV-326, the authors give

[31] According to the registration dossier, this substance is readily biodegradable but failing the 10 day window. It shows rapid dissipation in the aquifer test with a half-life of 5.3 days.
[32] This value is slightly below the range recommended in the OECD 308 TG.
[3333] OECD TG 308 outcome can be affected both by test vessel and system geometry and the associated water-sediment interface size (ECHA 2017). There is no specification of the vessel size or geometry in the test guideline, but the system geometry should be consistent with the range indicated in the OECD TG 308.
[34] For a discussion of the aerobic kinetics see below. The derivation of the anaerobic half-lives is not assessed further, but it is apparent from the graphs in the study that dissipation is indeed faster for the aerobic treatment. Potentially, another kinetic model might yield a better fit for the available data.

first-order dissipation half-lives of 52 days for the aerobic treatment. Dissipation half-lives for the anaerobic treatments are 72 days in the anaerobic control, 112 days under nitrate reducing conditions, 126 days under sulfate reducing conditions and 95 days under Fe(III) reducing conditions.

Aerobic treatment
In both the sterile and non-sterile samples, UV-326 was mainly present in sediment. In the sterile controls, the parent concentration in the test system remained constant during the test.

In the non-sterile treatments, a rapid growth of biomass was observed during the first 28 days, which might have been caused by the fast degradation of UV filters like benzophenone-3. During this initial phase of microbial growth, fast dissipation of UV-326 from the total system was observed, followed by a phase with significantly slower dissipation. The authors used first-order kinetics to calculate dissipation half-lives of 52 d for UV-326. A re-modelling conducted using the reported data (Cake 3.3, see Annex II) yielded acceptable statistics for some models but an unsatisfactory visual fit (see Annex II). The residuals confirm that a conclusion based on the data reported by this source should be made with caution as they are quite regularly distributed in every model. Due to these uncertainties, no modelled DT50 is preferred. Model results other than SFO reflect the slow dissipation observed after the initial phase of fast dissipation.[35] At an environmentally relevant temperature of 12 °C, this would correspond to half-life values that are larger, with temperature corrected slow phase DT50 values > 180 days.

As the substances were not radio-labelled, no information on the formation of non-extractable residues (NER) or transformation products is available. Based on the constant test concentrations in the sterile controls, no significant amounts of NER were formed in the sterile controls. As UV-326 does not dissipate in the sterile controls, its dissipation in the non-sterile tests appears to be associated with the presence of microorganisms.

The impact of the several deviations from the OECD TG 308 guideline on the study results is unclear. The following conditions may have contributed to the observed dissipation:

- In contrast to the study of Wick et al. (2016a, 2016b), this study has a sediment/aquifer with a low organic carbon content. The study on UV-384 described below shows rather fast dissipation of the structurally related metabolite M1 in the sediment with low organic carbon content, but DT50 >180 d for the sediment with high organic carbon content. Thus, the type of sediment may impact the observed dissipation.
- Co-metabolism might have occurred due to the presence of further substances, some of which are more readily biodegradable than phenolic benzotriazoles.
- The formation of non-extractable residues (NER) could have occurred in the sediment phase in the presence of microorganisms. The positive impact of microorganisms on NER formation is also reported in other studies (Botterweck *et al.*, 2014). The biomass growth promoted by other test substances might have contributed to this. No such effect was observed in the study of Wick et al. (2016a,

[35] Calculation results:

SFO DT50	DFOP		HS		FOMC	
DT50	DT50_fast	DT50_slow	DT50_fast	DT50_slow	DT50	DT90
52.4	19.5	>10,000	38.8	182	47.3	614

2016b). However, both studies show some characteristic differences.

- The test concentration of 1 mg/L or 1 µg/g per test substance[36] seems rather high, compared e.g. to the water-sediment studies of Wick et al. (2016a, 2016b) (10 µg/L in the supernatant). This might require significant growth of microorganisms to occur in order to obtain as high a decrease in test substance by degradation as observed in the study. Growth based kinetics could potentially explain the unexpected results. As significant microbial growth has occurred, (pseudo) first-order kinetics may not apply and the study is not appropriate for derivation of a degradation half-life.
- The location from which aquifer and water were sampled possibly resulted in the use of a pre-adapted microbial population. Both were drawn in the vicinity of the waste water treatment plant of Bolivar, a district of Adelaide, Australia that feeds its water into reservoirs for irrigation use. Exposition of the withdrawal site with phenolic benzotriazoles may have occurred beforehand as a complete withholding of particles in a wastewater treatment plant seems unrealistic.
- Several deviations from the OECD TG 308 guideline may have an impact on the study results, although there is no straightforward interpretation to explain the observed results. However, as mentioned above, results of the re-modelling were not satisfactory and the derived DT50 values should be treated with caution.

This study is considered as reliable with restrictions. Derivation of DT50 values is challenging. Testing conditions were designed to simulate aquifers and the test system does not correspond to common water sediment studies.

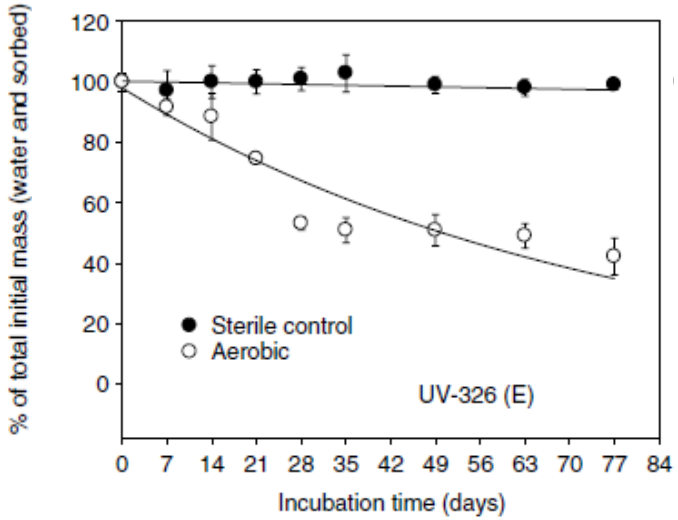


Figure 5: Dissipation of UV-326 (initial concentration of µg/g) in aerobic aquifer microcosms media. Error bars indicate standard deviations of the

[36] This corresponds to a total UV-filter concentration of 6 mg/L or 6 µg/g.

residual concentrations (n = 3) (Liu et al., 2013).

3.1.4.2.3.3 Study on UV-384 and its metabolite M1 in river and pond sediment systems

A detailed discussion of this study is given in the SVHC support documents for UV-328, UV-320, UV-327 and UV-350 (ECHA 2014a, ECHA 2014b, ECHA 2015a, ECHA 2015b). Therefore, only a short summary is provided here:

From the simulation studies on radiolabelled UV-384 (EC 407-000-3), the first metabolite of the substance (M1) is its carboxylic acid. M1 is structurally very similar to UV-326 (see beginning of section 3 on structurally related substances).

Two simulation tests for the substance EC 407-000-3 and its main metabolite M1 were evaluated. These tests were conducted according to OECD TG 308 at a test temperature of 20 °C. One test was done under aerobic conditions for a river system and a pond system, the other test was conducted under anaerobic conditions for a pond system. It was not possible to derive degradation half-lives for comparison with the trigger values as given in Annex XIII of REACH, but dissipation half-lives were derived. The absolute values for the pond system have to be interpreted with care as only part of the degradation curves of M1 were monitored.

Depending on the test system the observed dissipation half-lives DT50 for M1 varied:

- The aerobic river system had a low organic carbon content (0.95%); the DT50 values for M1 in the water and the sediment phase were 3 days and 32 days, respectively.
- The aerobic pond system had a high organic carbon content (5.04 %); the DT50 values for M1 in the water and the sediment phase were 4 days and 248 days, respectively.
- The anaerobic pond system had a high organic carbon content[37]; the DT50 values for M1 in the water and the sediment phase were 12 days and 238 days, respectively.

In summary, M1 has a DT50 > than 180 days both in the aerobic and in the anaerobic pond sediment, but a DT50 < 120 days in the aerobic river sediment.[38]

M1 is structurally similar to UV-326. Based on mechanistic considerations and biodegradation estimations it is expected that M1's susceptibility to degradation is similar or higher than that of UV-326 (DegT50(M1) ≤ DegT50(UV-326)).[39] As a consequence and based on structural similarities, it can be concluded that UV-326 is expected to have comparable degradation behaviour as M1 and thus it is expected to fulfil the vP criteria of REACH Annex XIII (DegT50 >180 days).

[37]The organic carbon content is not explicitly given, but the sediment is sampled from the same site as the aerobic pond, i.e. TOC is expected to be equal or at least similar.
[38] Correction to an environmentally relevant temperature of 12°C would lead to higher half-life values, but not to a difference regarding fulfilment of the P and vP criterion for freshwater sediment.
[39] All BIOWIN models predict a better biodegradability for M1 than for UV-326.
The CATALOGIC model 301C v12.17 predicts UV-326 and M1 to be not readily biodegradable. The extrapolated primary half-life values predicted with this model are 9 months 26 days for UV-326 and 1 year 3 months 26 days for M1. See also beginning of section 3 on structurally related substances for a more detailed comparison.

3.1.4.2.4 Field data with information from sediment cores

Table 14: Field data with information from sediment cores and related studies

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
Field study with dated sediment cores from Pearl River (Peng *et al.*, 2017)	Yes, covering parameters required for assessment.	Klimisch score 2	Adequate study for time profiles of sediment contamination, indicative of persistence in sediments.
Field study with dated sediment cores from Salem Sound & Narragansett Bay (Cantwell *et al.*, 2015)	Yes, covering parameters required for assessment.	Klimisch score 2	Adequate study for time profiles of sediment contamination, indicative of persistence in sediments.
Field Study with sediment cores from Pawtuxet River (all) & Narragansett Bay (UV-P, UV-327, UV-328) (Reddy *et al.*, 2000)	Yes, covering parameters required for assessment.	Klimisch score 2	Adequate study for time profiles of sediment contamination, indicative of persistence in sediments
Field Study with sediment cores from Pawtuxet River (Lopez-Avila and Hites, 1980)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Study for profiles of sediment contamination, adequacy limited because study is on structurally related substances and not on the target. Study supports findings of Cantwell *et al.*, 2015; Reddy *et al.*, 2000; White *et al.*, 2008.
Field Study with sediment cores from Narragansett Bay (Hartmann *et al*., 2005)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Study for profiles of sediment contamination, adequacy limited because study is on structurally related substances and not on the target. Study supports findings of Cantwell *et al.*, 2015; Reddy *et al.*, 2000; White *et al.*, 2008.
Field Study with sediment cores from Providence River & Narragansett Bay (Pruell and Quinn, 1985)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Study for profiles of sediment contamination, adequacy limited because study is on structurally related substances and not on the target. Study supports findings of Cantwell *et al.*, 2015; Reddy *et al.*, 2000; White *et al.*, 2008.
Field Study including sediment samples from Pawtuxet River (White *et al.*, 2008)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Adequate study for sediment contamination, supporting indication of persistence in sediments.
Field study including sediment cores from Providence River & Narragansett Bay but without profiles (Latimer and Quinn, 1996)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Adequacy limited because study is on structurally related substances and not on the target. Measured data for phenolic benzotriazoles are used as markers but not given in the study; study includes data on production history of phenolic benzotriazoles in Cranston, Rhode Island. Study supports findings of Cantwell *et al.*, 2015; Reddy *et al.*, 2000; White *et al.*, 2008.
Field Study (Jungclaus *et al.*, 1978)	Supporting, covering some parameters required for assessment.	Klimisch score 2	Study for contamination of water and sediment by industrial wastewater, adequacy limited because study is on structurally related substances and not on the target. Study supports findings of Cantwell et al., 2015; Reddy et al., 2000; White et al., 2008.

Sediment cores and detections related to sediment cores include information on whether pollutants emitted in the past are still detectable after a certain time span. The original exposure is often unknown. Detection of a substance in sediment layers dating back years or decades ago can be considered indicative of high persistence. In these cases, the concentration profiles can be considered to reflect past exposure. The lack of detection of a substance does not necessarily mean that it is not persistent.

Data are available for UV-326, UV-P, UV-327, UV-328, and UV-320. The phenolic benzotriazoles UV-327, UV-328, and UV-320 are structurally very similar to UV-326 (see beginning of section 3 on structurally related substances).

Observed concentrations are particularly high near point sources like the former chemical production plant at Cranston in Rhode Island. While the lower concentrations influenced by diffuse entries are of higher environmental relevance, the contaminated sites in Rhode Island are well-examined by a variety of studies and the high concentrations allow to study the fate of the substances more comprehensively.

3.1.4.2.4.1 Sediment cores from Pearl River

The Pearl River Estuary in China is influenced by diffuse sources. Peng *et al.* (2017) sampled sediment cores and analysed them for several pollutants, including the phenolic benzotriazoles UV-326, UV-P, UV-329, UV-327 and UV-328. Available data on sedimentation rate were used to estimate the year of deposition.[40] The sediment layers of detection of UV-326 date back several decades (covering the period 1965 to 2004), indicating very high persistence in sediment. As a comparison, the structurally related vP substances UV-327 and UV-328 were also detected. While UV-328 was reported in the publication as one of the more abundant UV absorbers, detected levels of UV-327 were

[40] The available sedimentation rate is based on radiometric dating, see https://doi.org/10.1016/j.scitotenv.2007.05.043 .

about 0.74-1.84 ng/g dw along C1 and trace level in some layers of C2 (Peng 2023).

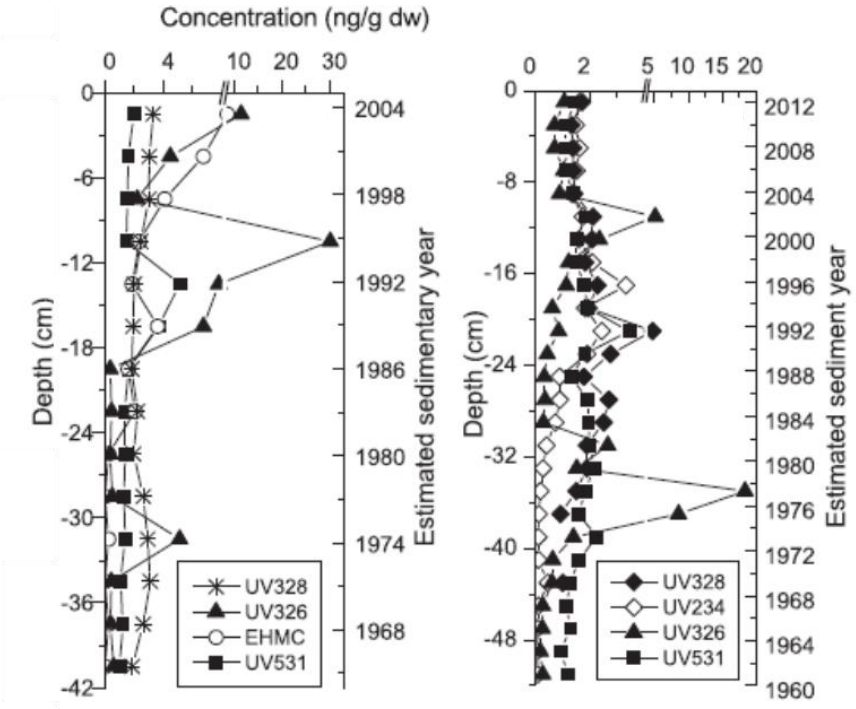


Figure 6: Vertical profiles of UV absorbents in the sediment cores C1 (left) and C2 (right) from the Pearl River Estuary (adapted from Peng *et al*., 2017).

3.1.4.2.4.2 Sediment cores from Salem Sound

Cantwell *et al.* (2015) studied benzotriazole contamination in Salem Sound, Massachusetts, USA. Salem Sound is an urban estuary not influenced by nearby benzotriazole production sites; sediment cores were sampled in May 2010 near the South Essex Sewage District outfall pipe. Radiometric dating was used to develop an age model. One sediment core was analysed for several phenolic benzotriazoles, among them UV-326. Results are depicted in Figure 7. The sediment layers from 11 cm depth to the surface of the core are considered undisturbed, while deeper sediment layers are considered affected by physical disruption.[41] The sediment layers of detection of UV-326 and other phenolic

[41] The presence of phenolic benzotriazoles in deeper sediment layers would correspond to decades prior to their production and thus, these findings indicate a past physical disruption of the sediment. However, based on radiometric data, there appears to be no significant post-sedimentation disturbance from 11 cm to the surface of the core.

benzotriazoles date back several decades, indicating very high persistence in sediment.

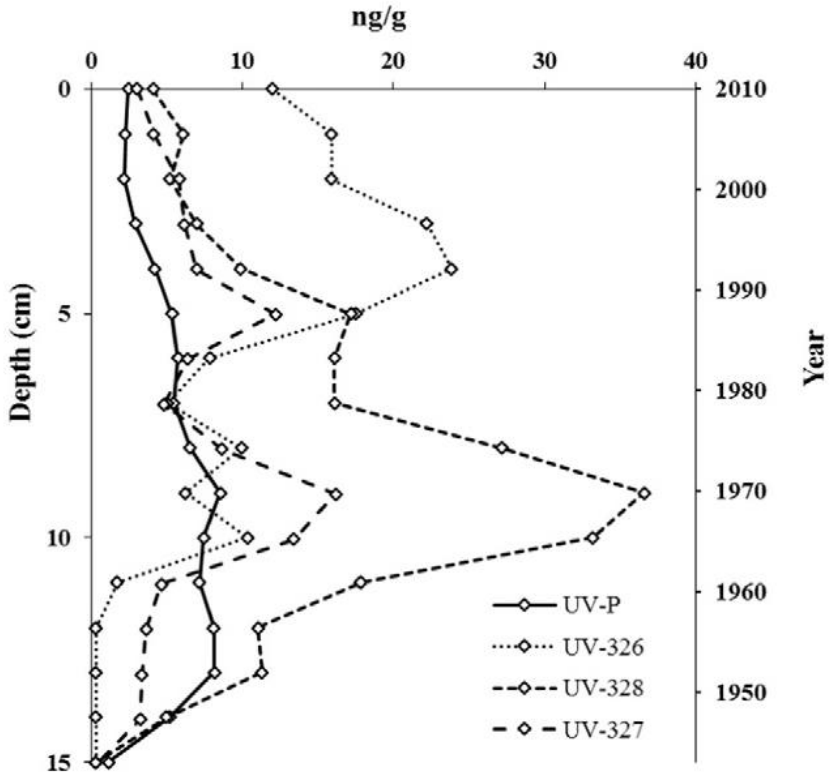


Figure 7: UV-Benzotriazoles in Salem Sound sediments (from Cantwell *et al.*, 2015).

3.1.4.2.4.3 Sediment cores and associated data from Pawtuxet River, Providence River and Narragansett Bay [42]

Until its closure in 1985 (Latimer and Quinn, 1996), a former chemical plant in Cranston, Rhode Island, USA discharged its industrial wastewaters in the Pawtuxet River. These wastewaters contained various chemicals produced at the plant, among them several phenolic benzotriazoles (Jungclaus *et al.*, 1978; Lopez-Avila and Hites, 1980). Consequently, contamination of Pawtuxet river sediments with phenolic benzotriazoles has been shown in several studies (Jungclaus *et al.*, 1978; Lopez-Avila and Hites, 1980; Reddy *et al.*, 2000; White *et al.*, 2008). Furthermore, these contaminated sediments from the Pawtuxet river are resuspended and transported, resulting in contamination of sediments downstream in the Providence River and the Narragansett Bay as well (Lopez-Avila and Hites, 1980; Pruell and Quinn, 1985;

[42] Except for the most recent study from Cantwell, these monitoring data have been discussed in the SVHC dossiers for UV-328, UV-320, UV-327 and UV-350 (ECHA 2014a, ECHA 2014b, ECHA 2015a, ECHA 2015b).

Latimer and Quinn, 1996, Reddy *et al.*, 2000; Hartmann *et al.*, 2005; Cantwell *et al.*, 2015).

Based on this set of studies, environmental contamination of this area with phenolic benzotriazoles is quite well-documented. Hence, studies on sediment cores from this area can use a comprehensive data set to support the interpretation of the analytical results. Based on the available data, UV-P, UV-327 and UV-328 appear to be the most abundant (Reddy *et al.*, 2000); UV-326 was detected in some studies as well (Reddy *et al.*, 2000; White *et al.*, 2008; Cantwell *et al.*, 2015; potentially[43] also in Lopez-Avila and Hites, 1980).

UV-P, UV-327 and UV-328 were used as markers along with other characteristic contaminants; known data on start and stop of production were used to estimate the age of sediment core sections (Lopez-Avila and Hites, 1980; Pruell and Quinn, 1985; Latimer and Quinn, 1996; Hartmann *et al.*, 2005). While the dating of these sediment cores is partially based on the substances themselves, the agreement with other markers indicates that they are present in sediment layers deposited years / decades before sampling.

White and co-workers (2008) analysed sediments from Pawtuxet River that were sampled in 2003, i.e., about 18 years after closure of the chemical plant. No phenolic benzotriazoles were detected in the sample upstream the chemical plant, while several phenolic benzotriazoles were detected in the samples downstream, including UV-326.

Two studies on sediment cores from this area are of particular interest:

Sediment core from Narragansett Bay with radiometric dating

Cantwell et al. (2015) studied benzotriazole contamination in a sediment core from Narragansett Bay that was sampled in October 2007. Radiometric dating was used to develop an age model. The sediment core was analysed for several phenolic benzotriazoles, including UV-326 (see Figure 9).[44] The results were compared with available data on production history: Sediment layers of detection of UV-326 and other phenolic benzotriazoles date back to 1961 when first patents for some of these compounds were documented. Phenolic benzotriazoles are also detected in sediment layers that correspond to the years after the production stop in 1985. The authors explain this by the transport of resuspended sediments from Pawtuxet River to the Bay. The concentration peak of UV-326 at ca. 1991 cannot be explained based on the available data and no comparable behaviour is observed for the other phenolic benzotriazoles examined in this study.

As expected, measured concentrations at Narragansett Bay were significantly higher as concentrations at the core from Salem Sound examined in the same paper and described above.

[43] Detected substance is given as 2-(hydroxy-tert-butyl methylphenyl)-5-chloro-2*H*-benzotriazole, a name which is not specific about the position of the hydoxy group, the t-butyl group and the methyl group. However, it is assumed that it is UV-326 as this is the only isomer known to be manufactured.
[44] UV-326, UV-P, UV-327, UV-328 and UV-320.

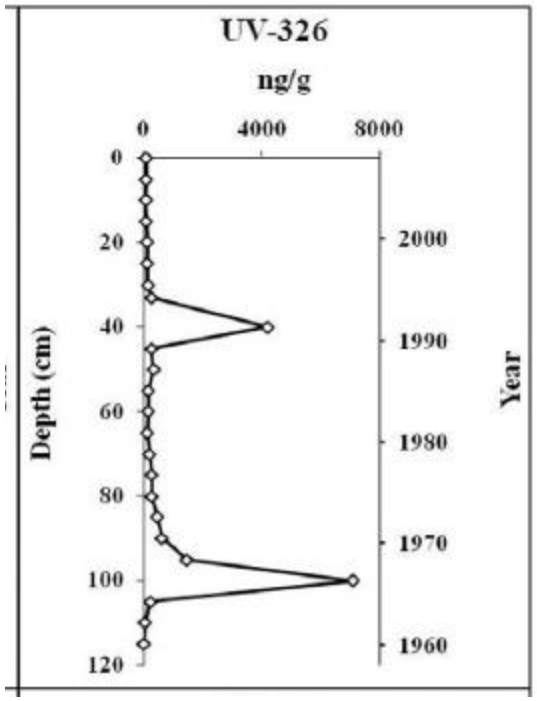


Figure 8: UV-326 in Narragansett Bay(from Cantwell et al. (2015)).

Sediment cores from Narragansett Bay and Pawtuxet River

Reddy *et al.* (2000) analysed two sediment cores for UV-326 and other phenolic benzotriazoles. Free and bound benzotriazoles were analysed and the ratio between free and bound benzotriazoles was discussed. The ratio of free to bound phenolic benzotriazoles varied depending on substance, sediment depth and location. The authors concluded that phenolic benzotriazoles without a substituent next to the hydroxyl group are more likely to bind to sediments. One of the cores had been sampled from Pawtuxet River and the other from Narragansett Bay. The core sections were not assigned to specific dates, but sedimentation rates of the sample locations were known and the authors estimate that the deepest core sections approximately date back to the start of phenolic benzotriazoles production, which they specify as about 1961-1970.

In the Narragansett Bay core, the most abundant phenolic benzotriazoles UV-P, UV-327 and UV-328 were significantly more concentrated than UV-326 and other phenolic benzotriazoles; only their results are presented in the study.

The sampling site at Pawtuxet River is closer to the chemical plant and the authors give a sedimentation rate of 2-3 cm/yr. The core was sampled in 1989. The deepest section with a depth of 52 cm to 50 cm would thus correspond to the years 1963-1964 (2 cm/yr) or to the

year 1972 (3 cm/yr), respectively. UV-326 was detected in sections up to a depth of about 20 cm, which would correspond to the years 1979 (2 cm/yr) or 1982 (3 cm/yr), respectively.

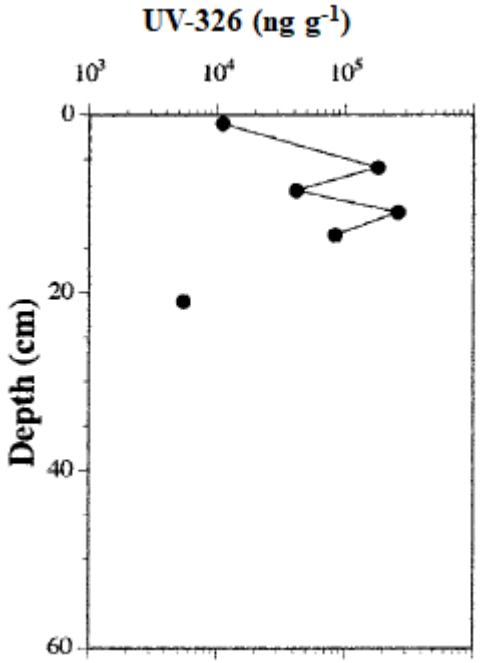


Figure 9: free UV-326 in the Pawtuxet River core (adapted from Reddy *et al.,* 2000).

Sediment core studies described above provide indirect evidence that UV-326 can persist in sediments for several decades.

3.1.4.3 Biodegradation in soil

3.1.4.3.1 Soil dissipation studies

Table 15: Soil dissipation studies

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
Soil dissipation study (Lai *et al.*, 2014a)	Yes, covering parameters required for assessment.	Klimisch score 2	Adequate study for dissipation in soil, indicative of persistence in soil
Soil dissipation study (Lai *et al.*, 2014b)	Yes, covering parameters required for assessment.	Klimisch score 2	Adequate study for dissipation in soil, indicative of persistence in soil

Lai and co-workers (Lai *et al.*, 2014a; 2014b) examined the dissipation behaviour of several phenolic benzotriazoles (UV-326, UV-329, UV-327, UV-328, and UV-P) in order to assess whether the application of biosolids as fertilisers in agricultural land might be a relevant pathway for environmental contamination.[45]

In the first study (Lai *et al.*, 2014a), dewatered sludge from a WWTP in Beijing was applied onto agricultural land in Shandong, China. The sludge was not further amended with reference substances or benzotriazoles meaning that all benzotriazoles were incorporated in it. In the first experiment (Treatment T1) this was done only once in May 2007 while in the second experiment (Treatment T2) application was repeated every year in October from 2007 until 2010. Each treatment consisted of application of the same dewatered sludge on four replicates. In addition, there was a control site where no treatments were conducted. In order to incorporate the sludge, the trial fields were ploughed to a depth of 20 cm. On the fields wheat and maize were cultivated.

Starting from October 2010 until October 2011, soil samples were taken monthly at a depth between 0 and 20 cm. Each sampling of the four replicates consisted of five subsamples that were mixed. Due to experimental problems this practice was stopped in winter and resumed in March 2011. The soil samples were extracted with methanol/dichloromethane (50:50, v/v) at 120 °C for 5 minutes in two cycles. Concentrations of the benzotriazoles were detected via GC-MS. The recovery in soil was 81.7% for UV-326. For UV-326 the limit of detection in soil was 0.2 ng/g and the limit of quantification in soil 0.67 ng/g.

At the beginning of the measurements (October 2010 to March 2011), considerable variability (i.e., a rise) of the concentrations was reported by Lai *et al*., 2014a. The authors attribute this to problems with obtaining a homogenous sample during the frost period or the degradation processes in samples during storage until extraction. No information is given if these were the reasons for the occurring variability and how this problem was finally solved. Beginning with March 2011 the problem was eliminated. In all the control samples only

[45] The first study (Lai *et al.*, 2014) has been discussed in the SVHC dossiers for UV-328, UV-320, UV-327 and UV-350 (ECHA 2014a, ECHA 2014b, ECHA 2015a, ECHA 2015b).

trace concentrations at the limit of quantification of UV-327 were detected, but other phenolic benzotriazoles were not found.

Due to the problem described above the authors performed a dynamic curve-fitting only between March 2011 and October 2011. They report the following times for field dissipation:

Table 16: Overview of reported DT50-values (dissipation in the field) by Lai *et al.* (2014a)

Substance	UV-326	
Treatment	**T1**	**T2**
DT50 [d]	104	141
Error [d]	10	17

The authors employed SFO-kinetics to derive DT50 values. As the treatments were carried out under highly similar environmental conditions, similar DT50-values are expected for T1 and T2.
For UV-326, DT50 values of 104 days and 141 days were determined for treatment 1 and treatment 2, respectively.

A detailed discussion of this study is given in the SVHC support documents for UV-328, UV-320, UV-327 and UV-350 (ECHA 2014a, ECHA 2014b, ECHA 2015a, ECHA 2015b).

A very similar study from the same authors on the same type of test soil at the same location is available (Lai *et al.*, 2014b). This study includes treatment groups with repeated biosolid applications every year (OT1, OT2, OT3, OT4), groups with biosolid applications only during the first year (NT2, NT3, NT4) and control sites. Field studies started in October 2006, with sampling conducted from October 2010 to October 2011.

The soil samples were extracted with methanol/dichloromethane (50:50, v/v) at 120 °C for 5 minutes in two cycles. Concentrations of the benzotriazoles were detected via GC-MS. The recovery in soil was 81.7% for UV-326. For UV-326 the limit of detection in soil was 0.1 ng/g and the limit of quantification in soil 0.32 ng/g.

The phenolic benzotriazoles were detected in all samples from sites with biosolid application, but not in the control groups. Concentrations of the target compounds increased from October 2010 to March 2011 – an effect observed in the other study (Lai *et al.*, 2014a) as well. Hence, in analogy to the approach from the related study, the authors performed dynamic curve fitting for the period of March 2011 to October 2011.

Table 17: Overview of reported DT50-values (dissipation in the field) by Lai *et al.* (2014b)

Treatment	Biosolid application [t ha^{-1}]	Substance UV-326
OT1	5 every year	90
OT2	10 every year	96
OT3	20 every year	128
OT4	40 every year	122
NT2	10 once	81
NT3	20 once	120
NT4	40 once	135

The observed dissipation shows variation with respect to the different treatments:

- For UV-326, modelled DT50 values in the different treatments ranged from 81 days to 135 days.

The results of these two soil dissipation studies have to be regarded as best cases for the disappearance in the environment as:

- they only reflect the warmer period of the year. Longer DT50s are expected during colder period of the year;[46]
- three (Lai et al 2014a) to four (Lai et al 2014b) years passed between (first) application and measurements, therefore potentially allowing microorganisms to adapt;
- only dissipation was monitored;
- NER were not considered at all.

The field studies of Lai *et al.* (2014a, 2014b) have some practical shortcomings: The concentrations of the different benzotriazoles in the sludge are missing and no initial concentration values for the different field trials after the first[47] applications of the biosolids are given. In addition, the limits of detection and quantification are quite high, at least compared to the concentrations found in some applications. To

[46] The average annual temperature of the site is 12.9°C but no information on seasonal variation is given. Furthermore, it is not specified whether the given temperature refers to air or soil. It can be assumed that the average temperature during the modelled timeframe was larger than 12°C and that a longer DT50 could be expected for the whole year.

[47] In case of repeated application, concentration values for the subsequent applications before October 2010 are missing as well.

assess the method, it would also have been helpful to determine the level of NERs.[48] Furthermore, the concentration values during the sampling time varied: for unknown reasons there was a rise in concentration levels during the winter months. This was solved by not considering them in the kinetic simulation, which in turn lowers the number of data points for fitting. Finally, it would have been helpful to employ a substance with known DT50 value as a point of reference. A shortcoming for the use in this dossier is that the study gives information on primary disappearance only, since none of the metabolites were determined.

Based on the above two field studies, it is concluded that UV-326 is persistent (and potentially very persistent) in soil (at least DT50 in soil >120 days).

3.1.5 Integration and Weighing of evidence (WoE analysis) and Application of Levels of Confidence

3.1.5.1 Abiotic Degradation

Based on general chemistry knowledge, UV-326 is not expected to be susceptible to hydrolysis. HYDROWIN does not find hydrolysable groups and CATALOGIC predicts no abiotic transformation under OECD 301 C testing conditions. Thus, all available lines of evidence support the assumption that the substance does not hydrolyse under environmental conditions.

Table 18: Integration and weighing of evidence for abiotic degradation

Type of Evidence	Consistency & Specificity	Likelihood/ Biological Plausibility	Temporality	Confidence / Strength of Evidence	Remaining Uncertainty
HYDROWIN	Prediction of hydrolysis, result consistent with general knowledge about hydrolysis of organic compounds	Plausible	Not relevant	low strength of evidence	Medium
CATALOGIC Abiotic	Prediction of abiotic transformation under OECD 301 C testing conditions; result consistent with general knowledge about hydrolysis of organic compounds	Plausible	Not relevant	low strength of evidence	Medium
Conclusion from overall confidence	No hydrolysis under environmental conditions (High/Medium Confidence)				

[48] No NER were observed in the water sediment tests (Wick et al 2016a, 2016b). Reddy et al. (2000) analysed free and bound phenolic benzotriazoles in sediments. Their results indicate that phenolic benzotriazoles can bind to sediment and phenolic benzotriazoles without a substituent next to the hydroxyl group are more likely to form a bound fraction.
In summary, the sediment data indicate that NER might be relevant in some cases.

The (Q)SAR predictions are not all valid as some of the predictions are not within the applicability domain. Thus, their overall weight is low. Based on general principles of chemistry, the chemical structure does not contain functional groups that are susceptible to hydrolysis. This finding is given the highest weight. In summary, it is concluded that the substance is expected to show no hydrolysis under environmental conditions with high confidence.

3.1.5.2 Biodegradation in aqueous media or aqueous environment

The (Q)SAR results can be considered as screening information and as prediction of ready biodegradability. Based on both EPISUITE and CATALOGIC results, the substance is not expected to be readily biodegradable.

While all CATALOGIC models predicted ultimate half-life values in the range of months or years, some predicted primary half-life values are in the range of days. However, the preferred model CATALOGIC 301 C v12.17 predicts a primary half-life value in the range of months.

UV-326 was found to be not readily biodegradable in the available screening tests.

For UV-326, no biodegradation after 100 days was observed in a water sediment study conducted at 20 °C, i.e., the respective DegT50 is >>100 days. The reference temperature for simulation tests is 12 °C[49], and degradation at 12 °C is expected to proceed even more slowly[50]. Application of the Arrhenius equation to extrapolate from 20 °C to 12 °C would result in a factor of about 2.12; i.e., the corresponding DegT50 at 12 °C would be >>212 days.

In an aquifer study (Liu 2013) conducted at 20 °C, observed dissipation was larger than expected based on the other data. Application of first order kinetics yielded a dissipation half-life of 52 d for UV-326, respectively. Other kinetic models indicate lower dissipation in the slow phase. The corresponding DT50 value at 12°C would be higher.

M1 is a structurally related substance to UV-326 and a metabolite of UV-384. Water sediment simulation studies on UV-384 showed that M1 is very persistent.

UV-326 and further phenolic benzotriazoles have been detected in sediment sections that date back years or even decades, both in samples downstream from a former point source and in samples from urban estuaries.
18 years after closure of a chemical plant, UV-326 was still detected in sediments sampled downstream the site, but not in sediment samples from upstream the site.

[49] ECHA 2017a. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT/vPvB assessment. Version 3.0, p. 59. https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf/a8cce23f-a65a-46d2-ac68-92fee1f9e54f (accessed February 2022)
ECHA 2017b. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7b: Endpoint specific guidance. Version 4.0, p. 219, 221-222. https://echa.europa.eu/documents/10162/13632/information_requirements_r7b_en.pdf/1a551efc-bd6a-4d1f-b719-16e0d3a01919 (accessed February 2022)
EC (European Commission). 2003. Technical Guidance Document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances and Commission Directive (EC) 98/8 on biocides. 2nd Edition, Luxembourg: European Commission.EC (European Commission) 2006, p. 49 and 53.
[50] Application of the Arrhenius equation to extrapolate from 20 °C to 12 °C would result in a factor of about 2.12. This would mean that DT50 >>212 days.

With exception of the aquifer study, all available lines of evidence support the assumption that UV-326 is very persistent in sediment.

Table 19: Integration and weighing of evidence for biodegradation in aqueous media or aqueous environment.

Type of Evidence	Consistency & Specificity	Likelihood/ Biological Plausibility	Temporality	Confidence / Strength of Evidence	Remaining Uncertainty
BIOWIN	Consistent predictions indicating the substances are not readily biodegradable	Plausible	Not relevant	Low strength of evidence	High
CATALOGIC	Consistent predictions indicating the substances are not readily biodegradable	Plausible	Not relevant	low strength of evidence	High
Biodegradation Screening test OECD TG 301B 2007, UV-326	Consistent experimental study indicating UV-326 is not readily biodegradable	Plausible	Not relevant	low strength of evidence	High
Biodegradation Screening test OECD TG 301C 1996, UV-326	Consistent experimental study indicating UV-326 is not readily biodegradable	Plausible	Not relevant	low strength of evidence	High
Biodegradation Screening test OECD TG 301B 1988, UV-326	Consistent experimental study indicating UV-326 is not readily biodegradable	Plausible	Not relevant	low strength of evidence	High
Water sediment simulation study (Wick A *et al.*, 2016a, 2016b)	Consistent experimental study indicating the substances are very persistent in sediment	Plausible	Not relevant	High strength of evidence	Low
Aquifer simulation study (Liu Y-S *et al.*, 2013)	Experimental study indicating the substance dissipates in an aquifer system under the specific conditions of the study , not consistent with other data; relevance	Limited plausibility: high stability of molecular structure and other experimental data on	Not relevant	Low/Medium confidence; low strength of evidence	Medium / High

	for natural aquatic sediment systems questionable	sediments show limited / no degradation			
OECD 308 Simulation study on UV-384 (EC 407-000-3) and its metabolite M1	Consistent experimental study indicating a structural analogue is very persistent in sediment	Plausible	Not relevant	Medium strength of evidence	Medium / Low
Field study with dated sediment cores from Pearl River (Peng *et al.*, 2017)	Consistent monitoring study indicating UV-326 is very persistent in sediment	Plausible	Not relevant	medium strength of evidence	Medium / Low
Field study with dated sediment cores from Salem Sound & Narragansett Bay (Cantwell MG *et al.*, 2015)	Consistent monitoring study indicating UV-326 is very persistent in sediment	Plausible	Not relevant	medium strength of evidence	Medium / Low
Field Study with sediment cores from Pawtuxet River (all) & Narragansett Bay (Reddy CM *et al.*, 2000)	Consistent monitoring study indicating UV-326 is very persistent in sediment	Plausible	Not relevant	medium strength of evidence	Medium / Low
Field Study with sediment cores from Pawtuxet River (Lopez-Avila V and Hites, RA 1980)	Consistent monitoring study supporting findings from Cantwell et al. and Reddy et al.	Plausible	Not relevant	low strength of evidence	Medium / High
Field Study with sediment cores from Narragansett Bay (Hartmann PC *et al.*, 2005)	Consistent monitoring study supporting findings from Cantwell et al. and Reddy et al.	Plausible	Not relevant	low strength of evidence	Medium / High
Field Study with sediment cores from Providence River & Narragansett Bay (Pruell RJ and Quinn, JG 1985)	Consistent monitoring study supporting findings from Cantwell et al. and Reddy et al.	Plausible	Not relevant	low strength of evidence	Medium / High
Field Study including sediment samples from Pawtuxet River	Consistent monitoring study indicating UV-326 is very persistent	Plausible	Not relevant	low strength of evidence	Medium / High

(White *et al.*, 2008)	in sediment				
Field study including sediment cores from Providence River & Narragansett Bay but without profiles (Latimer JS and Quinn, JG 1996)	Consistent monitoring study supporting findings from Cantwell et al. and Reddy et al.	Plausible	Not relevant	low strength of evidence	Medium / High
Field Study (Jungclaus GA *et al.*, 1978)	Consistent monitoring study supporting findings from Cantwell *et al.* (2015) and Reddy *et al.* (2000)	Plausible	Not relevant	low strength of evidence	Medium / High
Conclusion from overall confidence	UV-326 is very persistent in sediment (High Confidence)				

As the (Q)SAR models are trained on test results on ready biodegradability or - in the case of BIOWIN 3 and 4 - on expert judgement, they are considered as screening information with a low weight in the WoE approach for the P assessment of UV-326. Their results are consistent with the other data. UV-326 could be considered in the BIOWIN domain when following the recommendations of the User Guide, though the models are not trained on phenolic benzotriazoles. The CATALOGIC models include an automatic determination of applicability domain, which is much stricter. The preferred model includes some structurally related phenolic benzotriazoles in the training set. UV-326 is in the applicability domain of this one preferred model as it was part of the training set.

The available screening tests are considered valid and reliable. Their results are consistent with the other data. They are considered as screening information with a low weight in the WoE approach.

The water-sediment study for UV-326 shows slight deviations from OECD TG 308 but the impact of the deviations on the test is not considered detrimental. The results are consistent with the other data supporting the evidence that UV-326 is very persistent in sediment. The confidence level for this study is high and it is given the highest weight in the WoE evidence approach for the P assessment.

The aquifer study shows more dissipation than expected based on the other data. The study conditions represent aquifers rather than systems tested in common water sediment studies. Several deviations from the OECD TG 308 guideline may have an impact on the study results. Although there is no unambiguous interpretation to explain the observed results, results from the water-sediment simulation test on UV-384 and its degradation product M1 indicate that the applied sediment type may influence the observed dissipation. The value of the study for deriving information for water-sediment systems seems low. The confidence level for the aquifer study is low/medium and it is given a low weight in the WoE approach.

The water-sediment simulation studies on UV-384 indicate that the metabolite M1 is very persistent in sediment. This result is consistent with the other data. M1 is structurally similar to UV-326. Based on biodegradation estimations it is expected that M1's susceptibility to degradation is similar or higher than that of UV-326 (DegT50(M1) ≤ DegT50(UV-326)). As a consequence, and based on structural similarities, UV-326 is expected to have comparable degradation behaviour as M1 and thus it is expected to fulfil the vP criteria of REACH Annex XIII (DegT50 in sediment >180 days).
The confidence in the studies is high, but it is conducted for a structurally related substance. Thus, the overall confidence in this information is medium and it is given a medium weight for the assessment.

The confidence in the presence of UV-326 in aged sediment sections that date back years or even decades is considered high. The ongoing contamination at a former point source is considered as supporting evidence to the P assessment of UV-326. Monitoring data are used as supporting information in the WoE approach for UV-326. They are in line with the outcome of the water-sediment simulation study, the screening studies and the QSAR predictions as they point towards the persistence of UV-326 in sediments.

In summary, based on a weight-of-evidence approach it is concluded that UV-326 fulfils the P and vP criteria of REACH Annex XIII for the sediment compartment (DegT50 in sediment>180 days).

3.1.5.3 Biodegradation in soil

3.1.5.3.1 Soil dissipation studies

The two soil dissipation studies indicate that both substances are persistent and potentially very persistent in soil. This is consistent with the available screening information, with data on hydrolysis and with data on biodegradation in water sediment systems.

Table 20: Integration and weighing of evidence for biodegradation in soil (see Table 19 for screening data)

Type of Evidence	Consistency & Specificity	Likelihood/ Biological Plausibility	Temporality	Confidence / Strength of Evidence	Remaining Uncertainty
Soil dissipation study (Lai *et al.*, 2014a)	Consistent field study indicating the substance is persistent in soil	Plausible	Not relevant	Medium/high strength of evidence	Medium/Low
Soil dissipation study (Lai *et al.*, 2014b)	Consistent field study indicating the substance is persistent in soil	Plausible	Not relevant	Medium/high strength of evidence	Medium/Low
Conclusion from overall confidence	Persistent and potentially very persistent in soil (Medium Confidence)				

Ready biodegradability tests and QSARs show that UV-326 screens as P/vP (see Table 19 and section 3.1.5.2). These data are given a low weight.

The two soil studies are field studies and not equivalent to simulation tests. Their results describe dissipation. Confidence is medium/high and they are given a medium weight.

In summary, it is concluded that UV-326 fulfils the P criteria and potentially the vP criteria of REACH Annex XIII for the soil compartment (at least DegT50 in soil>120 days).

3.1.6 Uncertainty Analysis

No specific uncertainty analysis was considered necessary. The evidence was conclusive to decide on the vP properties of the substances. The evidence was of good quality and confidence levels were high.

No additional information is considered necessary.

3.1.7 Conclusions: Summary and discussion of degradation

The screening criterion for persistence (P) is fulfilled for the substance. The results from the available screening studies showed that the substances is not readily biodegradable. This is confirmed by the available (Q)SAR results.

Hydrolysis of the substance is not expected due to the absence of functional groups susceptible to hydrolysis.

In a water sediment simulation study at 20 °C, no degradation was observed after 100 days. At an environmentally relevant temperature of 12 °C this corresponded to a half-life significantly larger than 212 days.

Faster dissipation was observed in an aquifer test with specific conditions deviating from standard water sediment systems. The observed dissipation may be related to the different test conditions and the studied compartment compared to an OECD water-sediment simulation study. Simulation test results for a structurally related substance (M1) support both very high persistence in sediment for UV-326 and the impact of different sediment types on dissipation.

UV-326 and further phenolic benzotriazoles have been detected in sediment sections that date back years and even decades, both in samples downstream from a former point source and in samples from urban estuaries.

UV-326 is persistent (and potentially very persistent) in two soil dissipation studies.

As an overall conclusion, based on the above information used in a weight-of-evidence-approach, it is concluded that UV-326 meets the

'persistence' criterion (P) and the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and very persistent (P/vP) properties in sediment (DegT50 > 180 days). Furthermore, UV-326 meets the 'persistence' criterion (P) and potentially the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and potentially its very persistent (P/vP) properties in soil (at least DegT50 > 120 days).

3.2 Environmental distribution

3.2.1 Adsorption/desorption

The registration dossier for UV-326 contains (Q)SAR estimations of the adsorption potential. The KOCWIN program v2.00[51] was used to predict log K_{OC} values of 4.64 (MCI method) and 4.23 (log K_{OW} method) for UV-326. According to the information from the dossier, the substance is in the applicability domain of the models.

3.2.2 Volatilisation

Except for the vapour pressure given in section 1.4, no data are available on volatilisation. For screening purposes, the data matrix in Annex I contains QSAR predictions for Henry's Law constant. However, these QSAR results are not documented according to Anne XI of REACH and are the results should be treated with caution.
Based on the available data, volatilisation is not expected to impact degradation studies.

3.2.3 Distribution modelling

No data are available on distribution modelling.

3.2.4 Summary and discussion of environmental distribution

Based on the available log K_{OC} values, the substance is expected to adsorb to soil and sediment.

3.3 Data indicating potential for long-range transport

Not assessed.

[51] KOCWIN v2.00 in US EPA EPISuite v4.11.

3.4 Bioaccumulation

A weight-of-evidence assessment is carried out for bioaccumulation assessment. The "Weight-of-Evidence/Uncertainty Analysis Template[52]" is applied to structure the weight-of-evidence.

3.4.1 Bioaccumulation in aquatic organisms (pelagic & sediment organisms)

3.4.1.1 Screening data

In addition to the available experimental data, the log K_{OW} of the substances was estimated using COSMOtherm. [53]

Table 21: Available log K_{OW} data of the substance

Log K_{ow}	Method
6.7	COSMOtherm
≥ 6.5	OECD TG 117
7.38	experimental, Do *et al.* (2022)

COSMOtherm is an implementation of the COSMO-RS method. This approach has proven useful to predict a wide range of physico-chemical properties like liquid/liquid equilibria or solubilities (Klamt, 2011). The method is not a (Q)SAR but combines quantum chemical calculations and statistical thermodynamics. Consequently, there is no applicability domain in the classical sense. It is applicable to a much broader range of substances and the applied parameters are not specific of functional groups or molecule types (Eckert and Klamt, 2002).

The log K_{ow} values are above the screening trigger value of 4.5 for bioaccumulation. Consequently, UV-326 screens as potentially B/vB.

3.4.1.2 Aquatic bioaccumulation data

3.4.1.2.1 Problem formulation

A weight of evidence determination according to the provisions of Annex XIII of REACH is used to identify if UV-326 meet the criteria for B/vB in aquatic organisms.

[52] https://echa.europa.eu/documents/10162/17169198/template_for_weight_of_evidence_en.docx/eb183c2e-c360-cbce-7a58-ad2d1270e5bd
[53] COSMOconf conformer generation performed using the BP-TZVP-COSMO+GAS template; COSMOtherm property estimation performed using the BP_TZVP_21-parameterisation;
BIOVIA COSMOtherm, Release 2021; Dassault Systèmes. http://www.3ds.com;
BIOVIA COSMOconf, Release 2021; Dassault Systèmes. http://www.3ds.com

3.4.1.2.2 Collection and Documentation of all Information

Information/evidence used in the approach include:

- Experimental studies from endpoint study records from corresponding IUCLID Registration Dossiers and study reports
- Published Literature
- Research Project

Table 22: Collected information and documentation:

Source Name	Date of search	Type of information/evidence	Link/Reference	Keywords Searched	Reason for inclusion / exclusion from WoE approach
OECD TG 305-I UV-326 Study having the highest weight	-	Experimental Study	ECHA Dissemination website and study report	-	N/A

3.4.1.2.3 Assessment of quality of individual evidence

Table 23: Assessment of quality of individual evidence

Type of Evidence / Source Name - Reference	Relevance	Reliability	Adequacy
OECD TG 305-I (aqueous exposure) UV-326 Study having the highest weight	Study appropriate for investigation of aquatic bioaccumulation	Klimisch score 1 Reliable without restriction	Adequate on basis of reliability and relevance

3.4.1.2.3.1 Robust Study Summaries of Key Studies

OECD TG 305 with UV-326 (aqueous exposure)[54]

Study design and test conditions:

The study investigated the bioconcentration potential of UV-326 in juvenile rainbow trout (*Oncorhynchus mykiss*) according to the guideline

[54] ECHA Dissemination website and study report

OECD 305-I (aqueous exposure). The fish were exposed to one solvent control group (0.02 mL/L acetone) and one concentration group of test substance at 0.2 µg/L in a flow-through-system for an uptake period of 44 days followed by a depuration period in clean water of 63 days. In the interest of animal welfare this study used only one concentration of test substance to determine bioconcentration as recommended in the 2012 revised OECD 305 test guideline for non-polar organic chemicals. Scientific publications (Creton et al. 2013, Burden et al. 2014) provide compelling evidence that BCF values do not differ when multiple concentrations are tested.

Over the entire test all water quality parameters were maintained within acceptable limits. The pH was stable during the whole test period and was in a range of 8.0 – 8.2. The concentrations of dissolved oxygen were maintained in a range between 8.3 – 10.3 mg/L in the test vessels and were not less than 60% of the maximum saturation at the test temperature of 13 ±1°C during the test. The concentration of total organic carbon in the test vessels did not exceed the concentration of organic carbon originating from the test substance and solvent by more than 10 mg/L (± 20%). The test substance concentrations remained within ±20% of the mean of determined concentrations during the 44-day uptake phase. Only on day 42 of the uptake period the measured concentration (123.4%) was slightly higher than 20% of the mean of determined concentration but had no considerable influence on the overall mean measured results. No toxic effects (i.e., mortality) or changes in behaviour or appearance were observed in the test treatment organisms in comparison to the control group. In summary, all validity criteria were achieved.

The theoretical concentration and homogeneity during test substance preparation can be confirmed by the measurement of radioactivity from 3 different regions of the test solution tank via centrifuged and uncentrifuged test water samples prior to the start of exposure. Since there was a difference in the results of the concentration measurement between in centrifuged and uncentrifuged samples, in addition to concentration measurements of uncentrifuged samples also concentrations of centrifuged samples were measured as worst-case scenario in the subsequent analyses. The results of centrifuged samples were below 500 dpm/10 mL and should therefore be taken with care, since they are not fully reliable as the scintillator needs a minimum activity of 500 dpm/10 mL for calculation of reliable results, comparable to a limit of quantification (LOQ).

During depuration the concentration in test water samples were measured on three occasions and in fish on 10 occasions. Test substance concentrations in fish were determined on 9 occasions during uptake by measuring the total radioactivity. Total radioactive residues in fish were measured separately in edible (e.g., fillet) and non-edible (e.g., remaining carcass) portions and the whole fish value was calculated from the weight normalised sum of the individually measured portions. Measuring the concentrations in separate portions add uncertainties to the whole body BCF value. The bioconcentration factor was based on analyses of total radioactive residues in water and fish tissue thus also includes residues of possible metabolites of the test substance in the fish. The BCF calculated on the basis of these values therefore represents a worst-case assumption and might be lower if only the unmetabolized parent test substance is considered. Metabolite identification would certainly help to discriminate between metabolites, which may be slowly depurated (and thus contribute to the B-potential of the parent) and those that are rapidly excreted (e.g., glucuronide or sulfate derivates) from the body via liver, gall bladder or kidney (Arnot et al., 2018). UV 326 has an hydroxy group, which is relevant for phase II metabolism (i.e., conjugation with glucuronides and/or sulfates). This hydroxy group is less accessible as it forms a hydrogen bond to the nitrogen atom of the benzotriazole moiety. For UV 326 this hydroxy group may be hindered by large side chains next to it, preventing a fast metabolization (Leubner et al., 2023). Substituted compounds may be less metabolized compared to unsubstituted phenolic benzotriazoles in rats (Waidyanatha et al., 2021). UV-326 is disubstituted and metabolism in fish is expected to be in general lower than in rats. In conclusion, using the BCF values based on total radioactivity analysis for the B/vB assessment of UV-326 is considered acceptable.

Estimated results:

Since there was a statistically significant difference between the slopes of the growth rate, the test and control data were not pooled and a separate fish growth rate constant (k_g) of 0.0148 (± 0.004) day^{-1} for test group was calculated and used for "growth corrected" calculations. The lipid content of 2.8% was used for lipid correction.

The concentration in fish reached 95% steady-state within 44 days based on the kinetic calculations. Based on uncentrifuged test solutions, overall, the measured steady-state bioconcentration factor (BCF_{ss}) value (3559±561) was very similar to the calculated kinetic (BCF_K) value (3580) indicating that steady-state was reached, and that uptake and depuration follow first order kinetics. When normalised to a 5% lipid content in fish (using the mean lipid), the steady-state bioconcentration factor (BCF_{ssL}) was 6355 L/kg for the uncentrifuged test solution. Based on uncentrifuged test solutions, the lipid-normalised growth corrected bioconcentration factor BCF_{KgL} was 7093 for the whole fish based on total radioactive residues of the test substance. Based on centrifuged test solutions the BCF_{ss} was 7136±1124 L/kg. When normalised to a 5% lipid content in fish (using the mean lipid), the steady-state bioconcentration factor (BCF_{ssL}) was 12743 L/kg for centrifuged test solution and the bioconcentration factor BCF_{KgL} was 14225 L/kg for the whole fish based on total radioactive residues of the test substance.

This study is considered as reliable without restrictions.

Conclusion:

Based on this study, it can be concluded that UV-326 is very bioaccumulative with an estimated lipid-normalised and growth-corrected kinetic BCF value in the range 7093—14 225 L/kg (BCF>5 000, whole fish BCF back calculated from edible and non-edible portions and based on total radioactive residues of the test substance).

3.4.1.2.4 Integration and Weight of Evidence (WoE) analysis and Application of Level of Confidence

Table 24: Conclusion for aquatic bioaccumulation potential of UV-326

Type of Evidence	Consistency & Specificity	Likelihood/ Biological Plausibility	Temporality	Confidence / Strength of Evidence	Remaining Uncertainty
OECD TG 305-I with UV-326	Results are consistent with screening results, high specificity as substance specific BCF value is the result of the study and enables direct comparison with B/vB criteria of Annex XIII	Plausible	Not relevant	High	Low
Conclusion from overall confidence	As a standard OECD 305 BCF is available a direct comparison with the Annex XIII criteria for bioaccumulation is possible. The available BCF data give high confidence that UV-326 fulfills the B and vB criteria of REACH Annex XIII.				

3.4.2 Bioaccumulation in terrestrial organisms (soil dwelling organisms, vertebrates)

The substance might screen as potentially B in terrestrial organisms. This potential is, however, not fully assessed. In the following, some studies are summarised as supporting information.

Each of the many steps involved in the process of performing environmental studies described below will have an impact on the overall uncertainty of the final results. This uncertainty begins with the design of the sampling regime and is compounded through the entire process to storage of samples, chemical analysis and data treatment. As it is difficult to estimate the absolute uncertainty for all steps in the process the results are used in a more general way as supporting evidence in the bioaccumulation assessment.

3.4.2.1 Detection in breast milk

Lee *et al.* (2015)

Breast milk samples (n=208) were collected from 87 lactating women in the Children's Health and Environmental Chemicals in Korea Panel, or CHECK Panel. In this study, breast milk samples were collected from five Korean university hospitals located in four cities including Seoul, Pyeongchon, Ansan and Jeju, from February to December in 2011. The breast milk samples were divided into four groups at the following timepoints after delivery: <7, 15, 30, and 90 days postpartum. Participants completed questionnaire about current and previous pregnancy histories, medical history, and demographic parameters (age, BMI, parity, gestational age at delivery, sex of newborn, and delivery mode). Breast milk samples were collected in polypropylene tubes and were frozen and transported on ice to the laboratory. Samples were stored in the laboratory at −70 °C until analysis. Breast milk samples (10 mL) were extracted with 2.5 mL of 8% potassium oxalate solution, 10 mL of ethanol, and 5 mL of diethyl ether for 30 min by mechanical shaking and analysed with GC/MS. Among the BUVSs [benzotriazole UV stabilisers] analysed, UV-328 was dominant in all the samples, with a detection rate of 98%. The concentrations of UV-326 ranged from <2 to 53.1 ng/g lipid wt. in human breast milk with detection rate of 9.1%.

Kim *et al.* (2019)

Human breast milk samples (n=87) from primipara and multipara mothers were collected from

Kanagawa Prefecture, Japan (n=20) in 2009–2011, Malate (n=19) and Payatas (n=22), the Philippines in 2008, and Hanoi (n=7), Bui Dau (n=10), and Trang Minh (n=9), Vietnam in 2008. Informed consent was obtained from all the donors. The general information in the questionnaire included each mother's age, height, occupation, dietary habits, body mass index, birth procedure, and breastfeeding period, as well as the age and weight of the baby (Table 1). From each participant, about 100 mL of breast milk was collected using a breast pump to express milk into prewashed glass containers prepared for every individual. The collected milk samples in the Philippines and Vietnam except for Japan were shipped frozen to Japan and were stored at −25 °C in the Environmental Specimen Bank (es-BANK) of Ehime University until chemical analysis. Approximately 10 g of human breast milk samples were freeze-dried and then were extracted by High Speed Solvent Extractor (hexane/acetone, 1:1, v/v). Total concentrations of the 8 benzotriazoles in breast milk ranged from MDL (method detection limit) to 1100 ng/g lipid wt. in present study. Among the 8 benzotriazoles compounds targeted, the highest concentration of UV-9 was found in breast milk samples collected from Vietnam. The concentrations of UV-326 ranged from <MDL to 210 ng/g lipid wt. in human breast milk.

3.4.2.2 Detection in predators

Schlabach *et al.* (2018)

In this screening study about 90 different compounds with an array of physiochemical properties were measured in environmental samples. These samples included a selection of biota from localised hot-spot areas and from the most remote Arctic species. Biota samples were stored frozen (−20 °C) and extracted with organic solvents in an ultrasonic bath. UV-326 was detected in eggs of kittiwake (0.13 ng/g w.w., n=5, DF: 20%), blood of polar bear (0.31 ng/g w.w., n=5, DF: 10%), liver of American mink (0.37 ng/g w.w., n=5, DF: 100%). The UV filter UV-326 was found in Arctic hotspot biota. These findings suggest a potential to bioaccumulate and support earlier conclusions.

Lu *et al.* (2019)

Ringed seals were collected at Resolute Bay (n=3), Arviat (n=3), Sachs Harbour (n=3), and Lake Melville (n=5) by local hunters in 2016 and 2017 during subsistence harvesting. The livers of ringed seals were used for the present study. A mixture solvent of 5 mL 1:1 (v:v) hexane:dichloromethane was used to extract the sample. An ultra-performance liquid chromatography tandem mass spectrometer (UPLC-MS/MS) system was used for sample analysis. UV-326 was occasionally detected in the seal samples from Arviat, Sachs Harbour, and Resolute Bay regions. The concentrations of UV-326 ranged from <4100 to 6621 pg/g ww. in seal liver samples with detection rate of 0-33%. The detection suggests the presence of these contaminants in remote regions and resident species.

NILU reports: 20/2019 (Schlabach et al. 2022), 20/2021 (Heimstad et al. 2021)
The monitoring programme on behalf of the NILU-Norwegian Institute for Air Research provided results for various inorganic and organic environmental pollutants measured in different media and biological samples in the greater area of Oslo. Regarding the biotic samples UV-326 was detected in gull egg (20/2019: 0.17 ng/g, in 10 % of the samples), tawny owl (20/2021: 0.09 ng/g, in 67% of the samples), red fox liver (20/2021: 0.05 ng/g, in 67% of the samples) and brown rat (20/2021: 0.28 ng/g, in all samples). The absence of detection in monitoring studies is no contradicting evidence to the vB conclusion for the substances but rather may reflect low exposure in the area. Further explanation for absence of detection can be that LOD/LOQ values may set too high or analytical issues.

3.4.3 Summary and discussion of bioaccumulation

UV-326 screens as potentially B/vB due to log Kow values above the screening trigger value of 4.5.

As a standard OECD 305 BCF is available for UV-326 a direct comparison with the Annex XIII criteria for bioaccumulation is possible. The available BCF data give high confidence that UV-326 fulfils the B and vB criteria of REACH Annex XIII (BCF>5000).

Furthermore, UV-326 is detected in human breast milk and predators. As it is difficult to estimate the absolute uncertainty for the results of these studies they are used in a more general way as supporting information.

4 Human health hazard assessment

Not assessed.

5 Environmental hazard assessment

Not assessed.

6 Conclusions on the SVHC Properties

6.1 vPvB assessment

6.1.1 Assessment of vPvB properties

A weight of evidence determination according to the provisions of Annex XIII of REACH is used to identify the substance as vPvB substance. All available information (such as the results of standard tests, monitoring and modelling, information from the application of the category and analogue approach (grouping, read-across) and (Q)SAR results) was considered together in a weight of evidence approach.

6.1.1.1 Persistence

The screening criterion for persistence (P) is fulfilled for UV-326. The results from the available screening studies showed that this substance is not readily biodegradable. This is confirmed by the available (Q)SAR results.

Hydrolysis of the substance is not expected due to the absence of functional groups susceptible to hydrolysis.

In a water sediment simulation study at 20 °C, no degradation was observed after 100 days. At an environmentally relevant temperature of 12 °C this corresponded to a half-life significantly larger than 212 days.

Faster dissipation in an aquifer test may be related to the different sediment type tested or to the several deviations from standard conditions. Simulation test results for a structurally related substance (M1) support both very high persistence in sediment and the impact of different sediment types on dissipation.

UV-326 and further phenolic benzotriazoles have been detected in sediment sections that date back years and even decades, both in samples downstream from a former point source and in samples from urban estuaries.

UV-326 is persistent (and potentially very persistent) in two soil dissipation studies.

As an overall conclusion, based on the above information used in a weight-of-evidence-approach, it is concluded that UV-326 meets the 'persistence' criterion (P) and the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and very persistent (P/vP) properties in sediment (DegT50 > 180 days). Furthermore, UV-326 meets the 'persistence' criterion (P) and potentially the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and potentially their very persistent (P/vP) properties in soil (at least DegT50 > 120 days).

6.1.1.2 Bioaccumulation

UV-326 screens as potentially B/vB due to the available log K_{ow} values above the screening trigger value of 4.5.

As a standard OECD 305 BCF is available for UV-326 a direct comparison with the Annex XIII criteria for bioaccumulation is possible. The available BCF data give high confidence that UV-326 fulfils the B and vB criteria of REACH Annex XIII (BCF>5000).

The conclusion for UV-329 is based on a weight of evidence assessment using different pieces of information. The HYBIT BCF of >5000 is given the highest weight. HYBIT is a new test system and therefore is connected to some uncertainties regarding less experience in judging the results, especially k_1 values. To address these uncertainties especially for k_1 estimation from HYBIT test the project "Bioaccumulation assessment of superhydrophobic substances" was initiated, which supports the HYBIT BCF. *H.azteca* is an aquatic organism to which the B criteria of REACH Annex XIII refers to. Considering all evidence together especially the HYBIT test in combination with the related model predictions, recalculated fish BCF_{kgL} >2000 and the field data as supporting evidence UV-329 fulfils the B and vB criterion for aquatic organisms.

Furthermore, UV-326 is detected in human breast milk and top predators. This information is used in a more general way as supporting information.

6.1.2 Summary and overall conclusions on the vPvB properties

A weight of evidence determination according to the provisions of Annex XIII of REACH has been used to identify UV-326 as vPvB substance. All available relevant information (such as the results of standard tests, monitoring and modelling, information from the application of the read-across and (Q)SAR results) was considered together in a weight-of-evidence approach.

<u>Persistence</u>
The screening criterion for persistence (P) is fulfilled for UV-326. The results from the available screening studies (reliable with or without restrictions) showed that this substance is not readily biodegradable. This is confirmed by the available (Q)SAR results with BIOWIN and CATALOGIC which indicate that UV-326 screens as potentially P or vP. The outcomes of the screening tests and the (Q)SARs predictions have been assigned a low weight in the weight-of-evidence approach (WoE) for the P assessment.

Hydrolysis of UV-326 is not expected due to the absence of functional groups susceptible to hydrolysis. As a conclusion, abiotic degradation of UV-326 is not considered to be a significant degradation pathway in the environment.

In a water-sediment simulation study for UV-326 at 20 °C (reliable with restrictions), no

degradation was observed after 100 days. At an environmentally relevant temperature of 12 °C this corresponded to a half-life significantly larger than 212 days for UV-326 thus indicating its very persistent properties in sediment (DegT50>180 days). The outcome of this higher tier study is given a high weight in the WoE approach as it provides information directly comparable with the P and vP criteria set out in Annex XIII, points 1.1.1 (d) and 1.2.1 (b) of the REACH Regulation.

Faster dissipation of UV-326 in an aquifer test (reliable with restrictions) may be related to the different test conditions and the studied compartment compared to an OECD water-sediment simulation study. This study has been assigned a low weight in the WoE approach considering the studied compartment, the test conditions and the difficulty to derive an appropriate DT50. Simulation test results (reliable with restrictions) for a structurally related substance 3-[3-(2*H*-benzotriazol-2-yl)-5-*tert*-butyl-4-hydroxyphenyl]propionicacid (M1) *H*-support both very high persistence in sediment (DegT50 in sediment >180 days) for UV-326 and the impact of different sediment types on dissipation. This study on a structurally related substance is assigned a medium weight in the WoE approach.

UV-326 and further phenolic benzotriazoles have been detected in sediment cores that date back years and even decades (starting from the 1960s), both in samples downstream from a former point source and in samples from urban estuaries. This information provides indirect evidence that UV-326 can persist in sediments for several decades. Monitoring data in sediment cores are used as supporting information in the WoE approach for UV-326. They are in line with the outcome of the water-sediment simulation study, the screening studies and the QSAR predictions as they point towards the persistence of UV-326 in sediments.

UV-326 is persistent (and potentially very persistent) in two soil dissipation studies (reliable with restrictions) (at least DegT50>120 days).

As an overall conclusion, based on the above information used in a weight-of-evidence-approach, it is concluded that UV-326 meets the 'persistence' criterion (P) and the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and very persistent (P/vP) properties in sediment (DegT50 > 180 days). Furthermore, UV-326 meets the 'persistence' criterion (P) and potentially the 'very persistent' criterion (vP) in accordance with Annex XIII, points 1.1.1 and 1.2.1, of the REACH Regulation on the basis of its persistent and potentially their very persistent (P/vP) properties in soil (at least DegT50 > 120 days).

Bioaccumulation

Both UV-326 screens as potentially B/vB due to the available log K_{ow} values above the screening trigger value of 4.5.

An OECD TG 305 study (aqueous exposure; reliable without restriction) with rainbow trout (*Oncorhynchus mykiss*) performed on UV-326 indicates a high bioaccumulation potential with a lipid-normalised growth corrected kinetic bioconcentration factor (BCF_{kgL}) value in the range of 7093—14225 L/kg (whole fish BCF back calculated from edible and non-edible portions and based on total radioactive residues of the test substance). This study is given a high weight and its results are used to conclude that UV-326 has B/vB properties (BCF>5000 L/kg) in accordance with REACH Annex XIII. Monitoring data tend to confirm this prediction as UV-326 has been found in human breast milk and in biota including in top predators such as the polar bears which are listed as vulnerable to extinction, according to the International Union for Conservation of Nature (IUCN) Red List. Based on the weight of evidence of the data available, it is concluded that UV-326 meets the 'bioaccumulation' criterion (B) and the 'very bioaccumulative' criterion (vB) in accordance with Annex XIII, points 1.1.2 and 1.2.2, of the REACH Regulation.

Conclusion

In conclusion, UV-326 is identified as vPvB substance according to Art. 57(e) of REACH by comparing all relevant and available information listed in Annex XIII of REACH with the criteria set out in the same Annex, in a weight-of-evidence determination.

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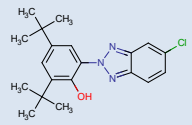
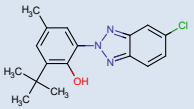
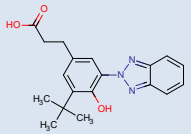
ANNEX I

Data matrix

Data matrix for UV-326, UV-327, M1.

Chemical name			UV-327[55]	UV-326	M1
EC number			223-383-8	223-445-4	630-348-4
Chemical structure					
Molecular weight			357.89	315.81	339.4
Impurities			None known	None registered (2 conformers)	None registered
Octanol water partition log K_{OW}			7.31 (Do et al. 2022) 7.85 (COSMOtherm)	≥ 6.5 (OECD TG 107) 7.38 (Do et al. 2022) 6.7 (COSMOtherm)	≥ 2.75 (OECD TG 107) 3.32 (COSMOtherm; log D)
Water solubility in µg/L			not available	4 (OECD TG 105)	< 1000 (OECD TG 105)
Estimated log K_{OC} (KOCWIN)			5.275	4.644	3.801
Vapour pressure at 20°C in Pa			not available	7.5 E-7 (exp)	2.9 E-10 (exp, 25°C)
HLC in atm-m3/mole (HENRYWIN)			2.74E-13	1.17E-13	1.56E-18
pK_a			10.07 (chemicalize)	10.18 (chemicalize)	9.31 and 4.25 (chemicalize)[56]
Hydrolysis			not expected	not expected	not expected
BIOWIN1 (Linear Model) Probability			0.1427	0.4013	0.6452

[55] Data on UV-327 added here as supporting information
[56] 19.08. 2023, https://chemicalize.com/ developed by ChemAxon (http://www.chemaxon.com)

Chemical name			UV-327[55]	UV-326	M1
BIOWIN2 (Non-Linear Model) Probability			0.0013	0.0235	0.197
BIOWIN3 numerical output			1.8338	2.0641	2.5832
BIOWIN4 numerical output			2.8989	3.0445	3.5614
BIOWIN5 (Linear MITI Model) Probability			-0.0095	0.065	0.4279
BIOWIN6 (Non-Linear MITI Model) Probability			0.002	0.0086	0.1056
CATALOGIC_301C_v12-17 BOD [28 days]			0	0	0
Ready biodegradability tests [28 days]			0% (OECD 301 C)	10-20% (OECD 301 B); 2-10% (OECD 301 B); 0% (OECD 301 C)	not available
Water sediment study (Wick et al 2016a, 2016b)			no degradation in 100 d	no degradation in 100 d	not tested
Aquifer system DT50			not tested	52 d	not tested
Rhode Island sediment cores (downstream Cranston chemical plant point source)			detected	detected	not analysed
Pear River Estuary sediment core (diffuse sources)			detected	detected	not analysed
Soil dissipation studies DT50			151-192 d; 112- 173 d	104-141 d; 81-135 d	not analysed

CATALOGIC results for M1

CATALOGIC 301C v12.17 is preferred because its training set contains the most phenolic benzotriazoles. The training set of CATALOGIC 301 C v12.17 contains UV-327 and consequently, this substance is in domain. The automatic applicability domain check shows that this model is also the best for M1 while it is still denoted "out of domain" due to 5% unknown fragments. If the default settings of the structural

domain for the model are changed to allow for unknown fragments with inert additions (meaning fragments that are not expected to have an impact), then also M1 would be 100 % within structural domain.

BIOWIN results for M1
Some BIOWIN results are contradicting; however, the reliability of these predictions is considered lower than the reliability of CATALOGIC 301C v12.17.

K_{OC}
The dossier for UV-326 contains KOCWIN predictions. For the sake of comparison, KOCWIN predictions[57] are given for the other substances as well. However, these predictions are not documented according to REACH Annex XI and hence, the respective results should be considered with caution. All considered substances are in the molecular weight range of training set and validation set. Correction factors for carboxylic acid groups and phenolic hydroxy groups were derived from training set substances with these structural features, i.e. though being dependent on pH, the ionic interactions of these groups may be covered by the model to a certain extent.

Henry's Law Constant
To estimate the expected impact of volatility on degradation studies, HENRYWIN predictions[58] are given for the substances. Note that these predictions are not documented according to REACH Annex XI and hence, the respective results should be considered with caution. All considered substances are in the molecular weight range of training set. The range of Henry's Law constants in the training set is exceeded by M1 which has a much lower Henry's Law constant. All other substances are in the Henry's Law constant range of the training set.

[57]2010 U.S. Environmental Protection Agency. KOCWIN v2.01 in EPISUITE v4.11.
[58]2010 U.S. Environmental Protection Agency. HENRYWIN v3.21 in EPISUITE v4.11. Bond method was applied; no results were obtained for the group method.

ANNEX II

Kinetic modelling for aquifer study Liu et al. 2013: UV-326

CAKE Kinetic Evaluation Report

Experiment 1 (SFO)

Model Setup:

Topology: Parent only
Optimiser: IRLS (IRLS Its. 10, IRLS Tol. 1E-05, Max. Its. 100, Tol. 1E-05)
Extra Solver Option: Use If Required

Initial Values of Sequence Parameters:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k_Parent	0.1	0 to (unbounded)	No

Fit step: Final

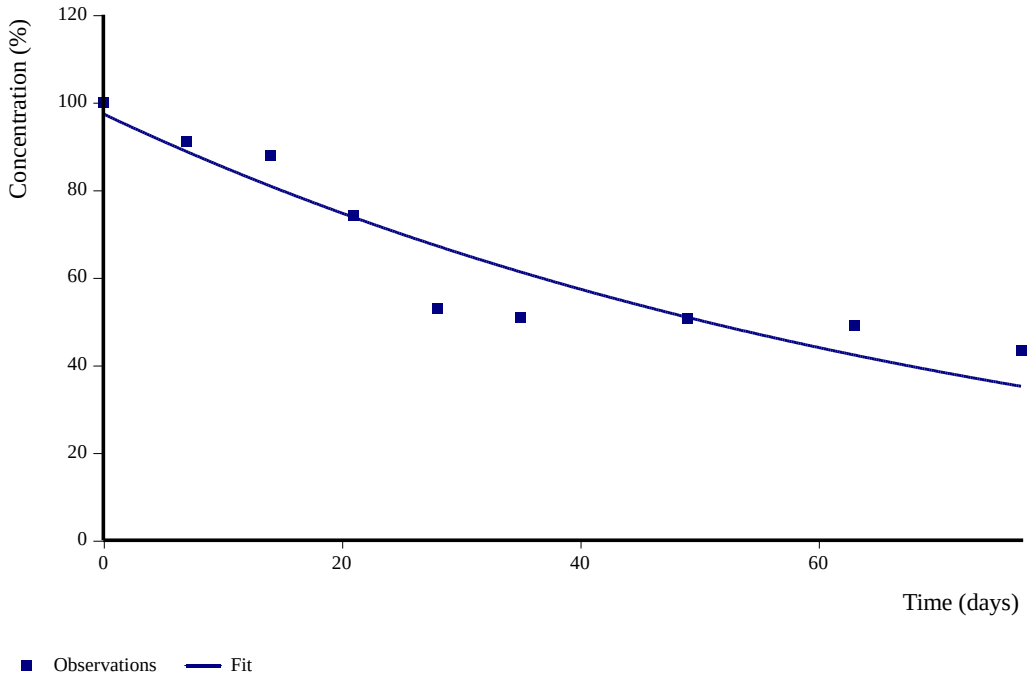
Used Extra Solver for SFO model fit: No

Reference Table:

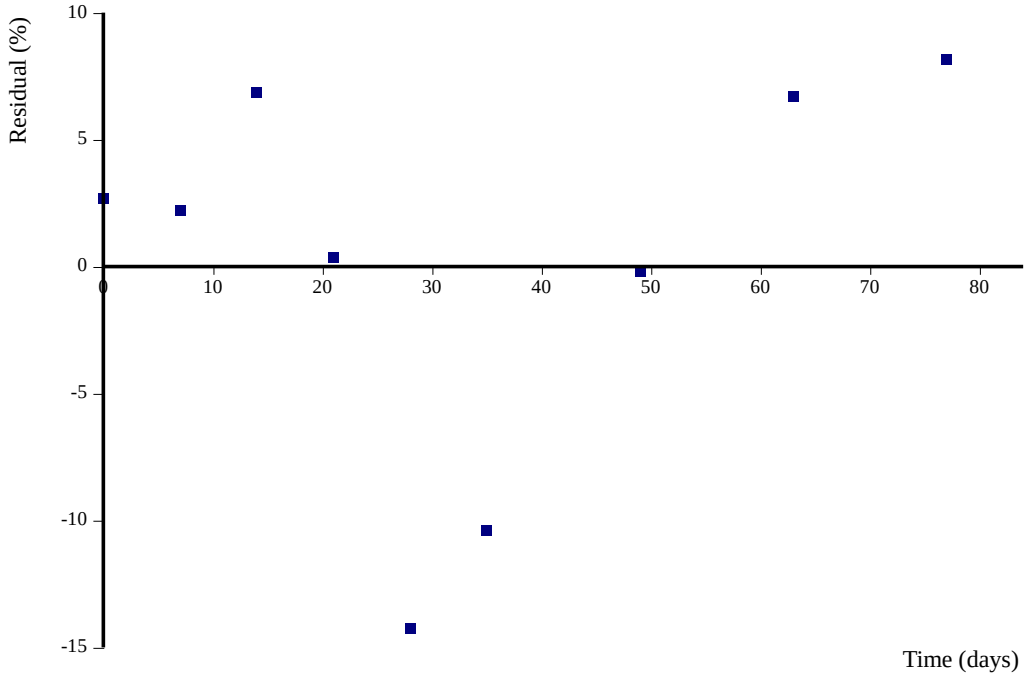
Compartment	Name
Parent	Parent

Graphical Summary:

Observations and Fitted Model:



Residuals:



Initial Values for this Step:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k_Parent	0.1	0 to (unbounded)	No

Estimated Values:

Parameter	Value	☐	Prob. > t	Lower (90%) CI	Upper (90%) CI	Lower (95%) CI	Upper (95%) CI
Parent_0	97.34	5.57	N/A	86.79	107.9	84.17	110.5
k_Parent	0.01322	0.002075	1.89E-004	0.009292	0.01715	0.008316	0.018

Sum of Squared Residuals: 482.3

χ^2

Parameter	Error %	Degrees of Freedom
All data	8.79	7
Parent	8.79	7

Decay Times:

Compartment	DT50 (days)	DT90 (days)
Parent	52.4	174

Additional Statistics:

Parameter	r² (Obs v Pred)	Efficiency
All data	0.8729	0.8713
Parent	0.8729	0.8713

Parameter Correlation:

	Parent_0	k_Parent
Parent_0	1	0.7164
k_Parent	0.7164	1

Observed v. Predicted:

Compartment Parent

Time (days)	Value (%)	Predicted Value	Residual

0	100	97.34	2.66
7	90.95	88.73	2.211
14	87.74	80.89	6.851
21	74.1	73.74	0.3601
28	52.96	67.22	-14.25
35	50.86	61.28	-10.42
49	50.72	50.92	-0.1999
63	49.02	42.32	6.703
77	43.33	35.16	8.165

Sequence Creation Information:
Fit generated by CAKE version 3.4 (Release)
running on R version 3.0.0 (2013-04-03)

Experiment 1 (DFOP)

Model Setup:

Topology: Parent only
Optimiser: IRLS (IRLS Its. 10, IRLS Tol. 1E-05, Max. Its. 100, Tol. 1E-05)
Extra Solver Option: Use If Required

Initial Values of Sequence Parameters:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k1_Parent	0.1	0 to (unbounded)	No
k2_Parent	0.01	0 to (unbounded)	No
g_Parent	0.5	0 to 1	No

Fit step: Final

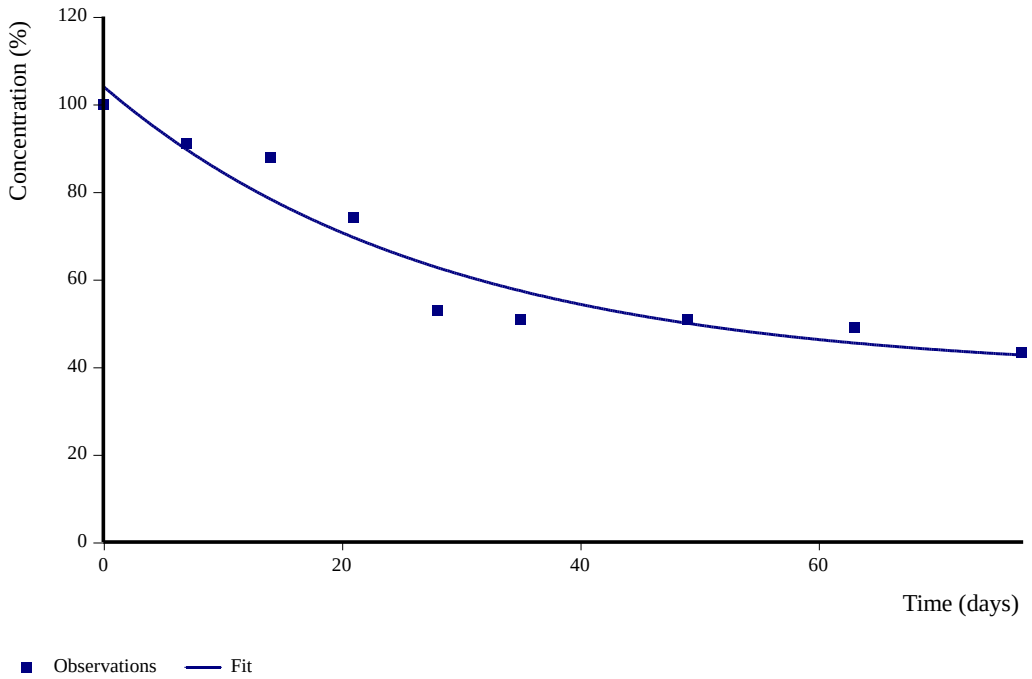
Used Extra Solver for DFOP model fit: No

Reference Table:

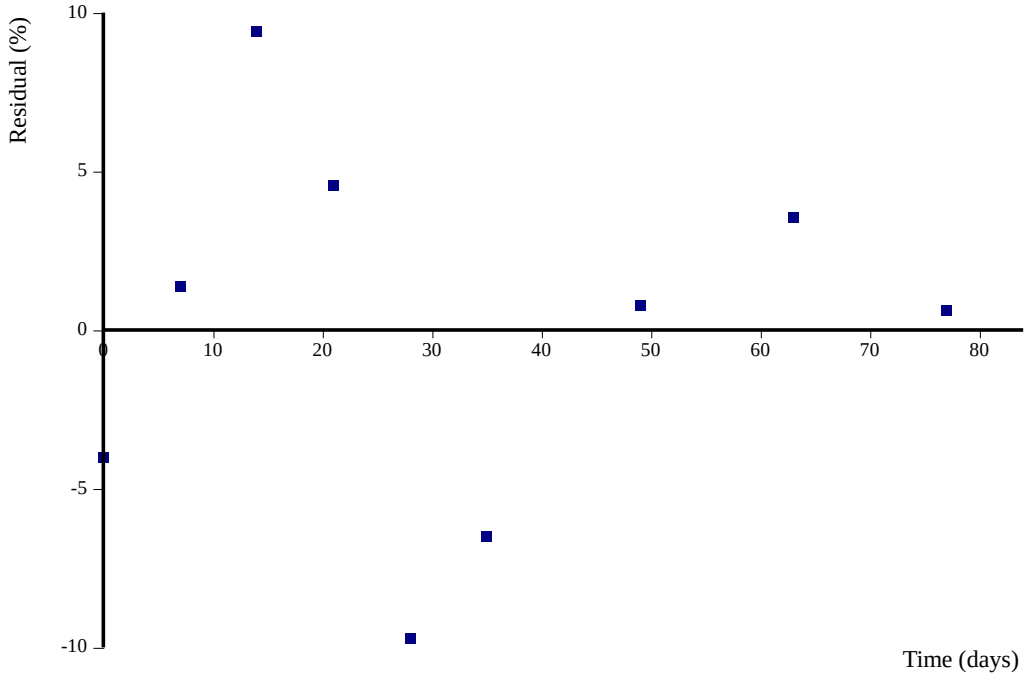
Compartment	Name
Parent	Parent

Graphical Summary:

Observations and Fitted Model:



Residuals:



Initial Values for this Step:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k1_Parent	0.1	0 to (unbounded)	No
k2_Parent	0.01	0 to (unbounded)	No
g_Parent	0.5	0 to 1	No

Estimated Values:

Parameter	Value	□	Prob. > t	Lower (90%) CI	Upper (90%) CI	Lower (95%) CI	Upper (95%) CI
Parent_0	104	6.97	N/A	89.98	118.1	86.11	121.9
k1_Parent	0.03554	0.05949	0.2881	-0.08434	0.1554	-0.1174	0.188
k2_Parent	5.09E-009	0.03152	0.5	-0.06352	0.06352	-0.08103	0.081
g_Parent	0.6302	1.104	N/A	-1.595	2.855	-2.208	3.469

Sum of Squared Residuals: 278.2

χ^2

Parameter	Error %	Degrees of Freedom
All data	7.52	5
Parent	7.52	5

Decay Times:

Compartment	DT50 (overall days)	DT90 (overall days)	k1 DT50 (days)	k2 DT50 (days)
Parent	44.4	>10,000	19.5	>10,000

Additional Statistics:

Parameter	r² (Obs v Pred)	Efficiency
All data	0.9258	0.9258
Parent	0.9258	0.9258

Parameter Correlation:

	Parent_0	k1_Parent	k2_Parent	g_Parent
Parent_0	1	0.4616	0.3439	-0.3507
k1_Parent	0.4616	1	0.9719	-0.9838

k2_Parent	0.3439	0.9719	1	-0.9968
g_Parent	-0.3507	-0.9838	-0.9968	1

Observed v. Predicted:

Compartment Parent

Time (days)	Value (%)	Predicted Value	Residual
0	100	104	-4.022
7	90.95	89.58	1.362
14	87.74	78.33	9.415
21	74.1	69.55	4.551
28	52.96	62.7	-9.738
35	50.86	57.37	-6.504
49	50.72	49.96	0.7624
63	49.02	45.46	3.563
77	43.33	42.72	0.6115

Sequence Creation Information:
Fit generated by CAKE version 3.4 (Release)
running on R version 3.0.0 (2013-04-03)

Experiment 1 (FOMC)

Model Setup:

Topology: Parent only
Optimiser: IRLS (IRLS Its. 10, IRLS Tol. 1E-05, Max. Its. 100, Tol. 1E-05)
Extra Solver Option: Use If Required

Initial Values of Sequence Parameters:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
alpha_Parent	0.1	0 to (unbounded)	No
beta_Parent	0.01	0 to (unbounded)	No

Fit step: Final

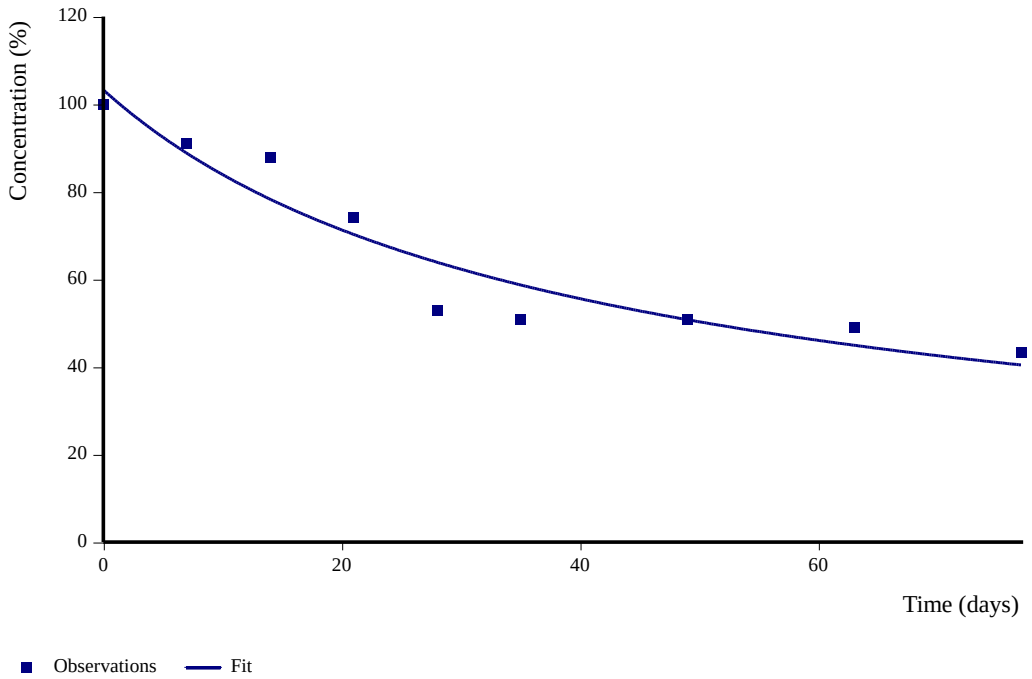
Used Extra Solver for FOMC model fit: No

Reference Table:

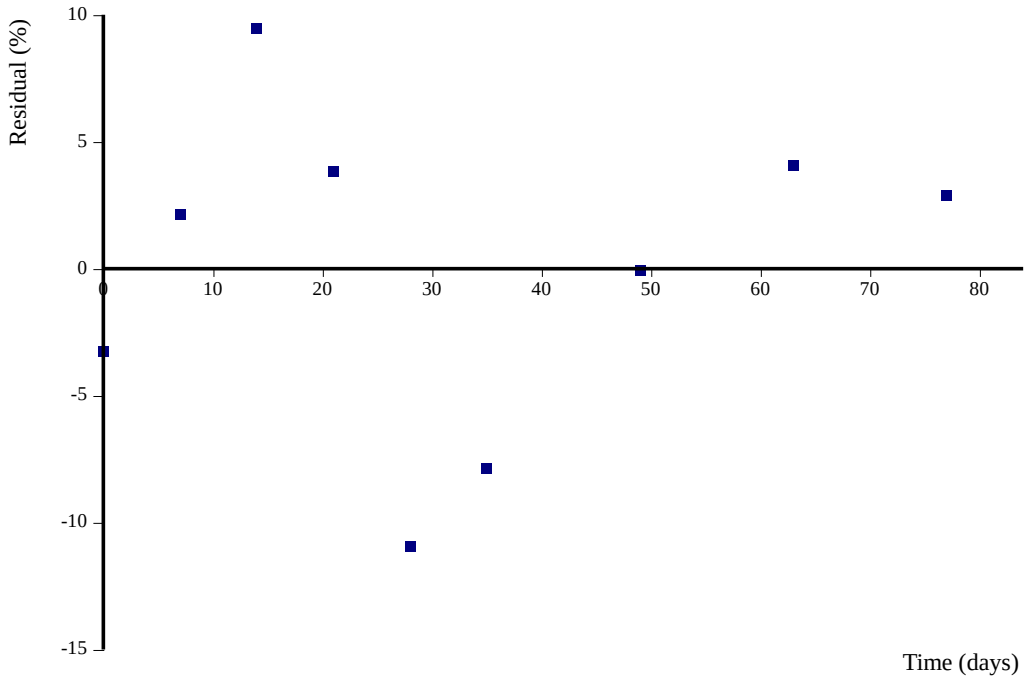
Compartment	Name
Parent	Parent

Graphical Summary:

Observations and Fitted Model:



Residuals:



Initial Values for this Step:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
alpha_Parent	0.1	0 to (unbounded)	No
beta_Parent	0.01	0 to (unbounded)	No

Estimated Values:

Parameter	Value	□	Prob. > t	Lower (90%) CI	Upper (90%) CI	Lower (95%) CI	Upper (95%) CI
Parent_0	103.2	6.867	N/A	89.91	116.6	86.45	120.1
alpha	0.7684	0.5806	N/A	-0.3597	1.897	-0.6522	2.189
beta	32.29	38.61	N/A	-42.73	107.3	-62.18	126.8

Sum of Squared Residuals: 325.6

χ^2

Parameter	Error %	Degrees of Freedom
All data	7.63	6
Parent	7.63	6

Decay Times:

Compartment	DT50 (days)	DT90 (days)	DT90 / 3.32 (days)
Parent	47.3	614	185

Additional Statistics:

Parameter	r² (Obs v Pred)	Efficiency
All data	0.9132	0.9131
Parent	0.9132	0.9131

Parameter Correlation:

	Parent_0	alpha	beta
Parent_0	1	-0.4618	-0.5772
alpha	-0.4618	1	0.985
beta	-0.5772	0.985	1

Observed v. Predicted:

Compartment Parent

Time (days)	Value (%)	Predicted Value	Residual
0	100	103.3	-3.249
7	90.95	88.8	2.147
14	87.74	78.29	9.454
21	74.1	70.26	3.841
28	52.96	63.9	-10.94
35	50.86	58.73	-7.867
49	50.72	50.79	-0.06763
63	49.02	44.95	4.068
77	43.33	40.46	2.873

Sequence Creation Information:
Fit generated by CAKE version 3.4 (Release)
running on R version 3.0.0 (2013-04-03)

Report Information:
Report generated by CAKE version 3.4 (Release)
CAKE developed by Tessella Ltd, Abingdon, Oxfordshire, UK, sponsored by Syngenta
Runtime: .NET Framework 4.8.4300.0

Data set: Experiment 1 (HS)

Study date: Mittwoch, 14. April 2021
Report generated: Mittwoch, 14. April 2021

Model Setup:

Topology: Parent only
Optimiser: IRLS (IRLS Its. 10, IRLS Tol. 1E-05, Max. Its. 100, Tol. 1E-05)
SANN Max Iterations: 10000
Extra Solver Option: Use If Required

Initial Values of Sequence Parameters:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k1_Parent	0.1	0 to (unbounded)	No
k2_Parent	0.01	0 to (unbounded)	No
tb_Parent	Automatic	0 to (unbounded)	No

Fit step: Final

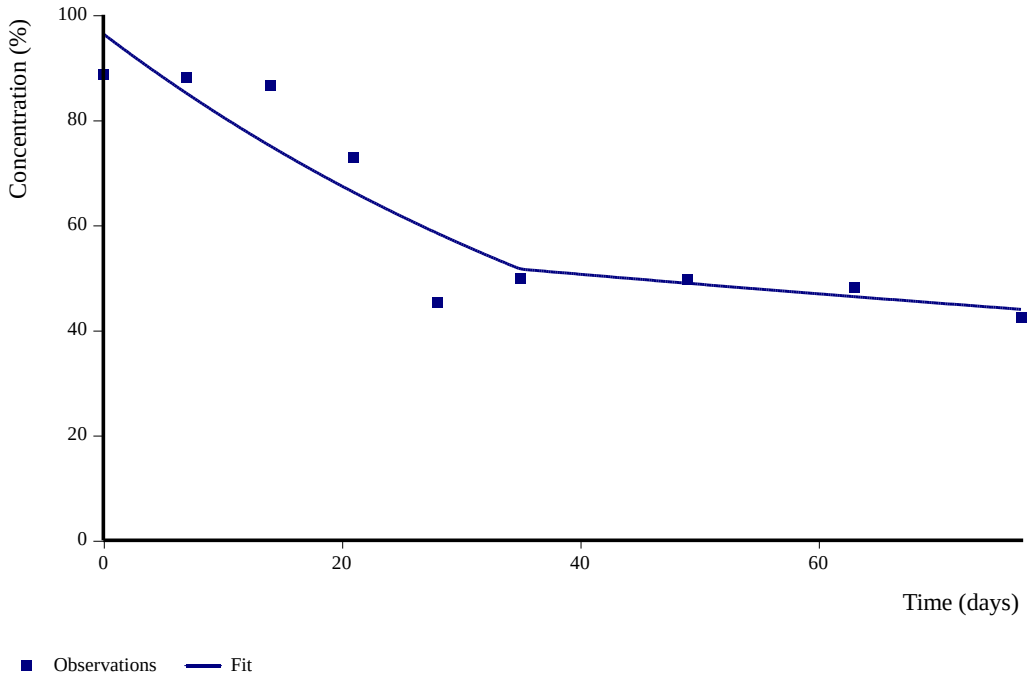
Used Extra Solver: Yes

Reference Table:

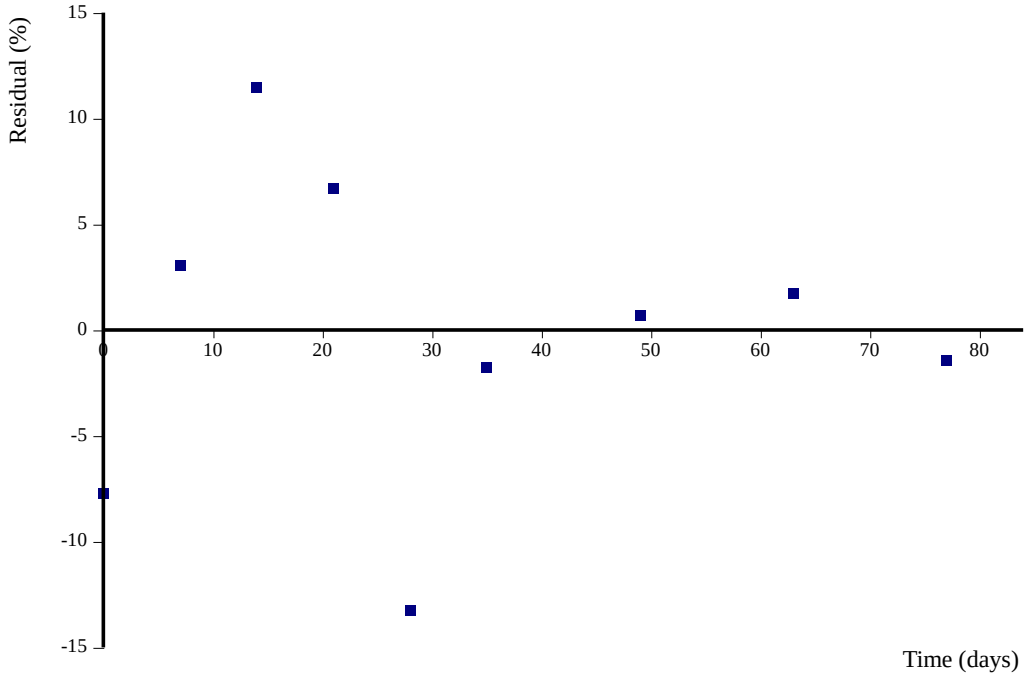
Compartment	Name
Parent	Parent

Graphical Summary:

Observations and Fitted Model:



Residuals:



Initial Values for this Step:

Parameter	Initial Value	Bounds	Fixed
Parent_0	100	0 to (unbounded)	No
k1_Parent	0.1	0 to (unbounded)	No
k2_Parent	0.01	0 to (unbounded)	No
tb_Parent	33.67	0 to (unbounded)	No

Estimated Values:

Parameter	Value	□	Prob. > t	Lower (90%) CI	Upper (90%) CI	Lower (95%) CI	Upper (95%) CI
Parent_0	96.34	7.243	N/A	81.75	110.9	77.73	115
k1	0.01785	0.00428	0.004371	0.009222	0.02647	0.006844	0.029
k2	0.003816	0.005229	0.2492	-0.006721	0.01435	-0.009626	0.017
tb	34.98	5.378	N/A	24.14	45.82	21.15	48.8

χ^2

Parameter	Error %	Degrees of Freedom
All data	9.81	5
Parent	9.81	5

Decay Times:

Compartment	DT50 (overall days)	DT90 (overall days)	k1 DT50 (days)	k2 DT50 (days)
Parent	53	475	38.8	182

Additional Statistics:

Parameter	r² (Obs v Pred)	Efficiency
All data	0.8678	0.8676
Parent	0.8678	0.8676

Parameter Correlation:

	Parent_0	k1	k2	tb
Parent_0	1	0.7354	-0.1761	-0.08203
k1	0.7354	1	-0.4723	-0.2256
k2	-0.1761	-0.4723	1	-0.2432

tb	-0.08203	-0.2256	-0.2432	1

Observed v. Predicted:

Compartment Parent

Time (days)	Value (%)	Predicted Value	Residual
0	88.6	96.34	-7.745
7	88.1	85.03	3.07
14	86.5	75.04	11.46
21	72.9	66.23	6.669
28	45.2	58.45	-13.25
35	49.9	51.66	-1.755
49	49.6	48.92	0.6797
63	48.1	46.38	1.724
77	42.5	43.96	-1.463

Sequence Creation Information:
Fit generated by CAKE version 3.3 (Release)
running on R version 3.0.0 (2013-04-03)

Report Information:
Report generated by CAKE version 3.3 (Release)
CAKE developed by Tessella Ltd, Abingdon, Oxfordshire, UK, sponsored by Syngenta
Running on .NET version 4.0.30319.42000