Substance Name: 2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328)

EC Number: 247-384-8

CAS Number: 25973-55-1

MEMBER STATE COMMITTEE

DRAFT SUPPORT DOCUMENT FOR

2-(2H-BENZOTRIAZOL-2-YL)-4,6-DITERTPENTYLPHENOL (UV-328)

Presented by the dossier submitter at MSC-30

14 June 2013

(Not concluded by MSC)

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FIGURES

Substance Name: 2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328)

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The substance is identified as PBT according to Article 57 (d) and as vPvB according to Article 57 (e).

Summary of how the substance meets the criteria set out in Articles 57(d) and 57(e) of REACH

Persistency:

According to a weight-of-Evidence argumentation UV-328 has to be considered vP and therefore also P.

Overview of the conclusions of the weight-of-evidence approach:

- ready biodegradation tests of UV-328 indicates a very low potential for biodegradation (2-6% after 28 days);
- Read-across assessment on EC 407-000-3 and its first metabolite: Very slow dissipation in aerobic systems (sediment and water) near or above the vP-trigger value based on data for the different compartments with and without temperature correction. Modelling of anaerobic system shows a DegT50 > 180 days already at 20°C. Degradation of the substances in question has to be even longer;
- For UV-327 and UV-328 there are monitoring studies available showing that the substances were found decades after environmental exposure has stopped. Model calculations indicate that these findings can only be explained if the $DegT_{50}$ is larger 180 days.
- Further supporting information:
    - Simulation of the complex degradation pathways gives a mechanistic explanation for similarities and findings;
    - Numerous findings in the environment in many different compartments and parts of the world although substances are used in small concentrations and overall tonnages are low.

Thus, applying the weight-of-evidence approach the substance fulfills the P and the vP-criterion of REACH Annex XIII

Bioaccumulation:

Based on the BCF study by CIBA (2010) and in light of all available data (e.g. Nakata et al. 2010) the substance fulfils the B and the vB criterion of REACH Annex XIII.

Toxicity:

Finally, UV-328 fulfils also the criteria to be classified as STOT-RE 2 and therefore has to be considered as toxic. Thus, the T-criterion of REACH Annex XIII is fulfilled.

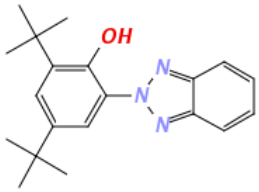
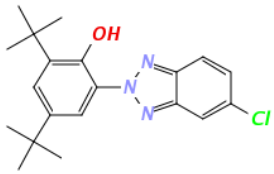
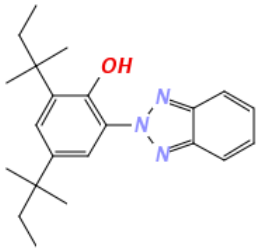
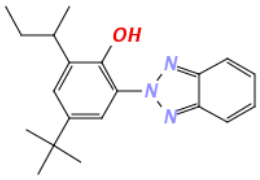
Conclusion:

In conclusion UV-328 meets the criteria for a PBT- and a vPvB substance according to Article 57d) and e).

Registration dossiers available: Yes

Note: This dossier is one of four dossiers for the SVHC-identification of several phenolic benzotriazoles as vPvB-substances and in two cases also as PBT-substances. Since these substances are structurally very similar and relevant data on individual substances for some endpoints is scarce, in these instances all information for all four substances of the set is given to allow an assessment based on read-across and a weight-of-evidence-approach in an analogue approach. All relevant available experimental data on the substances in question is presented in a read-across-matrix in Annex 1. In the individual chapters only the relevant data for assessing the individual endpoint will be presented. The set of the four phenolic benzotriazoles composes of:

Table 1: Overview of the phenolic benzotriazoles proposed for SVHC-identification

Name	**EC-nr.**	**CAS-nr.**	**Trade name used in this dossier**	**Structure**
2-benzotriazol-2-yl-4,6-di-tert-butylphenol	223-346-6	3846-71-7	UV-320	
2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol	223-383-8	3864-99-1	UV-327	
2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol	247-384-8	25973-55-1	UV-328	
2-(2H-benzotriazol-2-yl)-4-(tert-butyl)-6-(sec-butyl)phenol	253-037-1	36437-37-3	UV-350	

JUSTIFICATION

1 Identity of the substance and physical and chemical properties

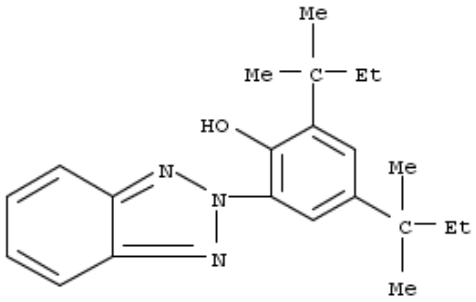
1.1 Name and other identifiers of the substance

Table 2: Substance identity

EC number:	247-384-8
EC name:	2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol
CAS number (in the EC inventory):	25973-55-1
CAS number:	25973-55-1
Deleted CAS numbers:	3142-41-4, 42558-99-6, 51829-45-9, 70419-42-0, 98354-04-2, 102257-30-7, 104817-16-5, 131242-53-0, 134018-57-8, 153613-73-1, 186805-09-4, 188025-36-7, 189377-89-7, 796971-88-5, 850346-35-9, 855281-45-7, 909728-30-9, 1244977-94-3, 1391942-68-9
CAS name:	Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)-
IUPAC name:	2-(2H-1,2,3-benzotriazol-2-yl)-4,6-bis(2-methylbutan-2-yl)phenol
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	$C_{22}H_{29}N_3O$
Molecular weight range:	351.50 g/mol
Synonyms:	Phenol, 2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentyl-(7CI,8CI) 2-(2-Hydroxy-3,5-di-tert-amylphenyl)-2H-benzotriazole 2-(2-Hydroxy-3,5-di-tert-amylphenyl)benzotriazole 2-(2-Hydroxy-3,5-di-tert-pentylphenyl)benzotriazole 2-(2H-Benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol 2-(2H-Benzotriazol-2-yl)-4,6-di-tert-pentylphenol 2-(2'-Hydroxy-3',5'-di-tert-amylphenyl)benzotriazole 2-(3,5-Di-tert-amyl-2-hydroxyphenyl)-2H-benzotriazole 2-(3,5-Di-tert-amyl-2-hydroxyphenyl)benzotriazole 2-(3,5-Di-tert-pentyl-2-hydroxyphenyl)-2H-benzotriazole 2-(3,5-Di-tert-pentyl-2-hydroxyphenyl)benzotriazole 2-(3',5'-Di-tert-amyl-2'-hydroxyphenyl)benzotriazole

	Chisorb 328 Cyasorb UV 2337 Eversorb 74 Kemisorb 74 Lowilite 28 Seesorb 704 Sumisorb 350 Tin 328 Tinuvin 328 UV 2337 UV-328 UV 74 Viosorb 591

Structural formula:



1.2 Composition of the substance

Name: 2-(2H-benzotriazol-2-yl)-4,6-bis(2-methylbutan-2-yl)phenol

Description: mono constituent

Degree of purity: >= 98%[1]

Table 3: Constituents

As this substance is a monoconstituent substance this information in not relevant.

[1] From C&L notifications

Constituents	Typical concentration	Concentration range	Remarks
2-(2H-1,2,3-benzotriazol-2-yl)-4,6-bis(2-methylbutan-2-yl)phenol EC-Nr.: 247-384-8			

Table 4: Impurities

Impurities	Typical concentration	Concentration range	Remarks
n.a.			

Table 5: Additives

Additives	Typical concentration	Concentration range	Remarks
n.a.			

1.3 Physico-chemical properties

Table 6: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	solid	
Melting/freezing point	80 – 83 °C	Estimated Value using EPIWIN Model (Syracuse Research Corporation, 2000)
Boiling point	477.84 °C	Estimated Value using EPIWIN Model (Syracuse Research Corporation, 2000)
Vapour pressure	0.0000000043 mm Hg at 25°C 0.000005 Pa at 20°C	Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20 Registration Dossier
Water solubility	0.042 mg/L 0.015 mg/L < 1µg/L at 20°C at pH 6.3 (The limit of quantitation of the analytical method of 10 µg/L corresponds to a limit of qualtitation of 0.5 µg/L for the samples (enrichment factor of 20). For practical reasons the results are stated as < 1 µg/L in all cases where no peak was detected)	Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20 Lopez-Avila, V & Hites, RA: EnvSciTechnol 11, p. 1382-1390 (1980) Source: Registration dossier;
Partition coefficient n-octanol/water (log value)	7.3 7.25 7.89 > 6.5 at 23°C, pH 6.4 (HPLC method)	Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20 EPISuite v.4.10 COSMOtherm v. C30_1201 Registration dossier

Dissociation constant	Most Basic: 8.85 at 25°C Most Acidic: 0.74 at 25°C	Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs)
[enter other property, if relevant, or delete row]		

Due to the weak dissociation potential the water solubility and the partition coefficient of the substance will be influenced by the pH value. This is because ions have other solubilities than the molecule. Therefore the pH value should be taken into account for evaluating the water solubility and the partition coefficient and further assessing of the hazard assessment. Unfortunately, it is not known if and when what pH-value was considered for the estimation of the physical and chemical properties.

2 Harmonised classification and labelling

No harmonised or agreed classification is available for the substance. The self classifications according to Regulation (EC) 1272/2008 (CLP) from ECHA's C&L Inventory database are provided in Annex 2 to give some indications on the hazards of the substance.

3 Environmental fate properties

3.1 Degradation

3.1.1 Abiotic degradation

3.1.1.1 Hydrolysis

The chemical bond between the benzotriazole group and the aromatic ring is generally expected to be very strong and also able to withstand degradation due to hydrolysis (see also 3.1.2.1.1) and also the aliphatic groups in the side chains of the phenol ring are functional groups that are expected to be generally resistant to hydrolysis. Due to the high log K_{OW} and the high adsorption potential to organic carbon the substance will adsorb to sewage sludge and suspended organic matter when it is released to the sewage treatment system respectively to the aquatic environment.

Therefore hydrolysis is not expected to be a relevant pathway of elimination of UV-328.

3.1.1.2 Phototransformation/photolysis

Phenolic benzotriazoles are mainly used as an UV-absorber. This means that on the molecular level UV-radiation excites the phenolic benzotriazole. In this excited state a proton from the OH-group is transferred to a nitrogen atom. From this structure a radiationless deactivation coupled with another proton transfer from the nitrogen back to the OH-group will bring the molecule back into its ground state. The UV-protection properties are based on this fully reversible and non-destructive process. Therefore degradation through photolysis can be

regarded as a negligible degradation path, nevertheless the different compartments will be briefly discussed.

3.1.1.2.1 Phototransformation in air

An estimation for half-life in air due to degradation with OH-radicals has been conducted with AOPwin v1.91 (US EPA, 2011) assuming a 12 hour-day and a OH-concentration of $1.5*10^6$ OH-radicals/cm³. The reliability of the results from the QSAR was rated Klimisch 2.

The atmospheric half-life was estimated to be 8.14 hours, the overall OH-rate constant was estimated to be $1.58*10^{-11}$ cm³*molec^{-1}*sec^{-1}.

It is expected that photodegradation in air is no relevant pathway for removal from the environment. As it is assumed that the majority of UV-320 will be emitted indirectly via sewage treatment systems and directly via surface runoff into the aquatic compartment and considering the very low vapour pressure of UV-328 it was concluded that the substance will not evaporate at ambient temperature. This assumption is supported by the results of environmental distribution modelling (please see section 3.3.2). Therefore photolytic degradation in the atmosphere is not considered to be relevant for the PBT assessment in the light of the partition properties of the substance.

3.1.1.2.2 Phototransformation in water

Photolytic degradation of UV-328 is expected to be a relevant degradation process only in very shallow clear waters and in the first few centimetres of the water column, decreasing rapidly in the lower layers of the water column, if at all. It is expected that the environmental exposure of UV-328 occurs in the whole water column. Because of the substance's adsorption potential it will predominantly bind to suspended organic matter and sediment which is supposed to significantly decrease the availability of the substance for photolytic degradation.

This leads to the conclusion that photolytic degradation in the natural aquatic environment is not considered having a relevant impact on the overall persistency of UV-328.

3.1.1.2.3 Phototransformation in soil

Information from industry indicates that a small fraction of the group of phenolic benzotriazoles is used in the EU in cosmetic products. The majority of this fraction will end up in waste water and finally adsorb to sewage sludge. As the use of this sludge is a common practice in agricultural industry soil will be subject to indirect exposure. As final step the sludge will be ploughed in and therefore only negligible quantities will be available for photolytic degradation processes.

This leads to the conclusion that photolysis is not a relevant pathway for removal of UV-328 in soil.

3.1.2 Biodegradation

3.1.2.1 Biodegradation in water

3.1.2.1.1 Estimated data

To the dossier submitter's knowledge no studies exist describing the biodegradation pathway of the phenolic benzotriazoles in the environment. Therefore the pathways of all phenolic benzotriazoles in question were simulated with the University of Minnesota Biocatalysis/Biodegradation Prediction System (UM-PPS[2]). This web application is a rule- based system currently encompassing 250 microbial biotransformation rules based on over 1350 microbial catabolic reactions and about 200 biodegradation pathways. The system compares the organic functional groups of the entered molecules with its set of rules and shows all possible degradation steps. The reaction steps are color coded according to the likelihood that the respective reaction is catalysed by certain bacteria in water, soil or sediment. An overview of the system can be found in two recent publications by Ellis et al. (Ellis et al., 2008) and Gao et al (Gao et al., 2011). Please note that it is not possible to predict rate constants with this system. Also there is no defined applicability domain for this rules based system.

As the phenolic benzotriazoles are complex molecules, their degradation pathway is also quite complex. Nevertheless a comparison of the results shows similarities and patterns. To better understand the degradation processes some generalizations are helpful. For all four phenolic benzotriazoles on which dossiers were submitted three different degradation pathways are possible. The first one starts at the phenol ring of the benzotriazole moiety. While the phenol ring is degraded, this degradation pathway always ends when a triazole group is left. The second possibility is to start the degradation at the side chain in position four (para-position) to the hydroxyl group. This degradation pathway ends when the side chain is completely degraded. For the complete degradation of the phenolic benzotriazoles the third degradation pathway is the most relevant, as this one results in the degradation of the bond between the phenol ring and the benzotriazole moiety which is never directly cleaved. The UM-PPS predicts that the actual breakdown of the phenolic ring begins only when two vicinal hydroxyl groups on the phenolic ring are formed. In order to obtain the vicinal hydroxyl groups it is necessary to degrade the side chain in position six (ortho-position) first. Depending on the phenolic benzotriazole in question this encompasses many reaction steps that sometimes are not very likely (and therefore kinetically speaking slow). Of special importance in this regard is the transformation of the aliphatic methyl groups into primary alcohols. The crucial step after degradation of the side chain is reached when the two vicinal hydroxyl groups are formed. Then the carbon-carbon-bond between them is broken and therefore the phenolic ring is cleaved. The mechanism is shown in Figure 1. In the actual degradation of the phenolic benzotriazoles all three possible degradation pathways will coexist and it is a question of the individual molecular structure of the metabolite which pathway is the kinetically most favorable. For the assessment the process was simplified by choosing the pathway that is most likely and shortest. However, it has to be noted that the rules of the UM-PPS were not explicitly derived for cleavage of phenolic rings bound to benzotriazole and therefore it is uncertain if the mechanism proposed by UM-PPS is relevant in the environment.

[2] http://umbbd.msi.umn.edu/predict/ (accessed 12.06.2012)

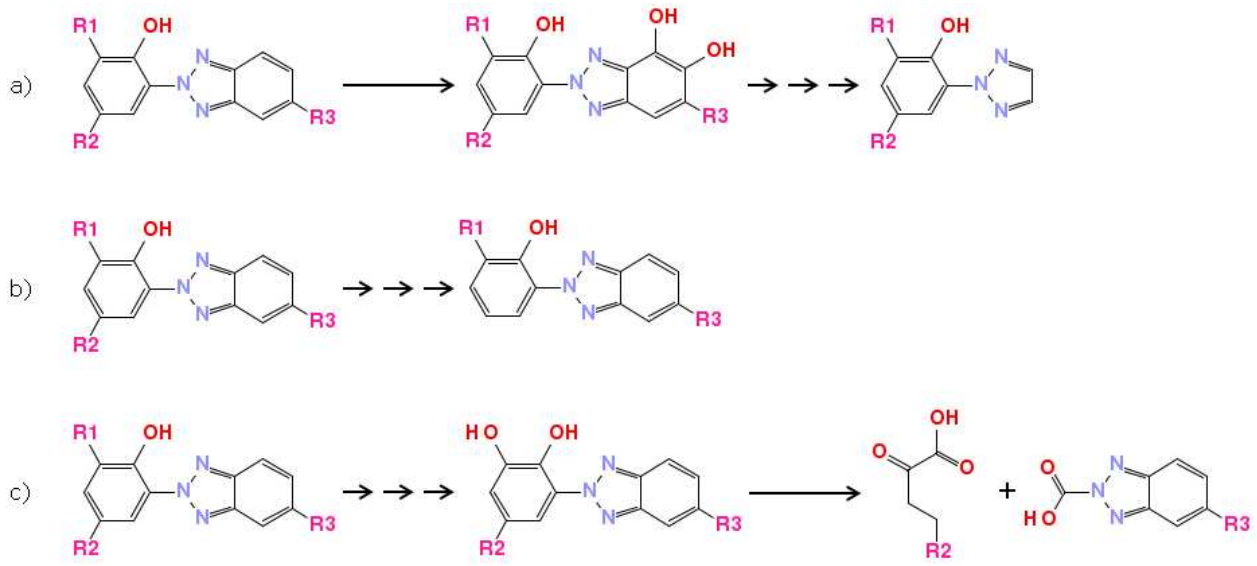


Figure 1: Proposed simplified mechanisms for the degradation of the phenolic benzotriazoles. a) Degradation of the benzotriazole moiety; b) Degradation of side chain R2; c) Degradation of side chain R1 leading to the ringcleavage of the phenolic ring R1, R2: alkyl; R3: H or Cl. Side reactions are for the sake of simplicity not considered here.

In Annex 3 an overview of the reaction pathways of all substances assessed in this chapter as predicted by the UM-PPS is given.

In summary, with our current knowledge on the mechanism of the biodegradation of phenolic benzotriazoles, it seems reasonable to assume that they will be degraded slowly in the environment, especially if the position six is substituted with a complex side chain that has to be degraded stepwise before ring cleavage of the phenol ring can occure.

To get a first impression on the actual potential for biodegradation an estimation of the biodegradation behaviour was then done with BioWIN v4.10 (US EPA, 2011):

- Biowin2 (non-linear biodegradation probability) results in a value of 0.0108 indicating that the substance does not biodegrade fast.
- Biowin6 (MITI non-linear biodegradation probability) results in a value of 0.0096 indicating that the substance is not readily degradable.
- Biowin3 (Survey model – ultimate biodegradation) results in a value of 2.0546 indicating that the degradation will take several months.

3.1.2.1.2 Screening tests

An assessment on the biodegradation behaviour of UV-328 was completed by The Phenolic Benzotriazoles Association within the framework of the High Production Volume (HPV) Challenge Program of the United States Environmental Protection Agency (U.S. EPA) in 2009. A study following OECD Guideline 301 B (Readily Biodegradability: Modified Sturm Test; volume of test solution was reduced from 3.0 litres to 1.5 litres; reliability rated Klimisch 2) was conducted. The parameter followed for biodegradation estimation was CO_2-evalution. After the test duration of 28 days the concentrations of the residues revealed a degradation rate in the samples between 2 (initial substance concentration: 20 mg / l) and 6 percent (initial substance concentration: 10 mg/ l). Therefore the submitting legal entity draws the conclusion that the substance is not biodegradable according to the OECD definition (The Phenolic Benzotriazoles Association, 2001). These results agree with the predictions of BIOWIN and the

proposed complex degradation pattern.

3.1.2.1.3 Simulation tests

No simulation tests of the four phenolic benzotriazoles in question are available to the dossier submitter. However, dissipation and degradation of the substance EC 407-000-3 (Reaction mass of branched and linear C7-C9 alkyl 3-[3-(2-H-benzotriazol-2-yl)-5-(1,1-dimethyl)-4-hydroxyphenyl]propionates) in a water-sediment study according to OECD 308 was examined (dossier on 407-000-3). This study was used for a read-across on the persistence of the four phenolic benzotriazole.

Rationale for read-across asessment:

According to REACH regulation Annex XI 1.5 (Grouping of substances and read-across approach). The aim of a read-across according to REACH is to avoid testing of every substance for every endpoint, by using data known for one substance – in this case of the environmental fate - for other, similar substances. Substance similarity may be based on three criteria:

(1) a common functional group;

(2) common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties. This criterion is of special relevance when using a grouping approach whichis not done here.

Nevertheless, all three points are met: EC 407-000-3 is a phenolic benzotriazole as the four substances that are assessed in these documents. It is substituted in the positions four and six of the phenol ring just like the four substances in question. Both substitution groups are alkyl chains. Position six is substituted with a tert-butyl-group which is also present in UV-320, and UV-327. In UV-328 there is a tert-pentyl-group, the next higher homologue of a tert-butyl-group in this position. In case of UV-350 a sec-butyl-group is in position six, which is a structural isomer of a tert-butyl-group. Position four of the substances UV-320, UV-327 and UV-350 is again substituted with a tert-butyl-group, while it is substituted by a tert-pentyl-group in case of UV-328. EC 407-000-3 is substituted in position four of the phenolic ring with a propionic ester. The difference between UV-320 and UV-327 lies in a chlorine atom on the benzotriazole moiety. In summary the five substances are structurally very similar.

Not only are the substances themselves similar, but also the breakdown products are similar. The possible degradation processes for the four substances were already discussed in chapter 3.1.2.1.1. The most likely degradation pathway for EC 407-000-3 was also simulated with UM-PPS. The simplified degradation pathway is shown in Annex 3. The whole pathway follows the same pattern as observed for the four substances of interest: At first the ester is degraded in its carboxylic acid (in the following called M1, see Figure 2). Then the side chain in position four is degraded stepwise. It ends up with one of the breakdown products that are also possible for UV-320. The subsequent degradation steps are therefore the same.

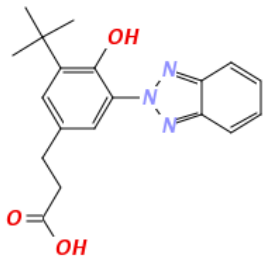


Figure 2: M1 (CAS 84268-36-0) is the first metabolite of degradation of EC 407-000-3

Based on the chemical composition of the substitution groups of the four phenolic benzotriazoles and M1 a qualitative estimation of the expected degradation times can be made:

$DegT_{50}(M1) < DegT_{50}(UV\text{-}350) < DegT_{50}(UV\text{-}328) \approx DegT_{50}(UV\text{-}320) \approx DegT_{50}(UV\text{-}327)$

The rationale can be seen in the fragment approach of Table 7.

Table 7: Fragments to be considered for qualitative assessment of degradation times.

Substance	R1	R2	R3
M1	tert-butyl	n-propionic acid	H
UV-350	sec-butyl	tert-butyl	H
UV-328	tert-pentyl	tert-pentyl	H
UV-320	tert-butyl	tert-butyl	H
UV-327	tert-butyl	tert-butyl	Cl

Therefore the degradation M1 can be regarded as a best case-scenario for the degradation half life times of the four phenolic benzotriazoles.

In conclusion the REACH criteria for applying a read-across approach are met and the degradation study of EC 407-000-3 can be used as further supporting information on degradation behaviour of the phenolic benzotriazoles.

Assessment of a a water-sediment study according to OECD 308 on EC 407-000-3 (aerobic conditions)

Test conditions are generally well described and the test was done according to GLP but validity descriptors remain unknown or even question reliability of the study, i.e. Chi^2 is not reported and many graphs do not sufficiently match the responding values. The report is reliable with restrictions (2 according to Klimisch).

As usual for this kind of study two systems of different organic carbon levels were employed. A river system contained low level and a pond system contained high level of organic carbon. Sampling locations of water and sediment were a pond and the river Rhine. For both systems the sampling locations were thought to not have been pre-exposed to the test substance or

structural similar substances. The pond did not receive effluent discharge and this was assumed for the river Rhine, too, but as no exact sampling location was given some uncertainty remains. The test substance was radiolabelled in the benzene ring of the triazole moiety. Test systems were allowed to acclimatise for two weeks after filling. Test duration was 100 days and test temperature was 20 ± 2 °C. As this is higher than 12°C the PBT guidance recommends to employ a temperature correction with a Q10-factor of 2.2. Please note that this factor was derived for degradation not dissipation, where it might be lower. Water sediment ratio was 3.3:1. A stock solution which consisted of test substance in aceton was stepwise diluted to give a final concentration of the test substance of 3 µg/L. The test substance was applied dropwise onto the water surface. Water and sediment were separated and analysed at each sampling point. Two traps were employed for volatile substances. On six occasions samples were taken and analysed. Analysis was done by TLC, HPLC and LSC and recovery rate was 98.7 % (96.2-101.2 %) for the river system and 99.9 % (97.6-101.9 %) for the pond system (see Figure 3 and Figure 4).

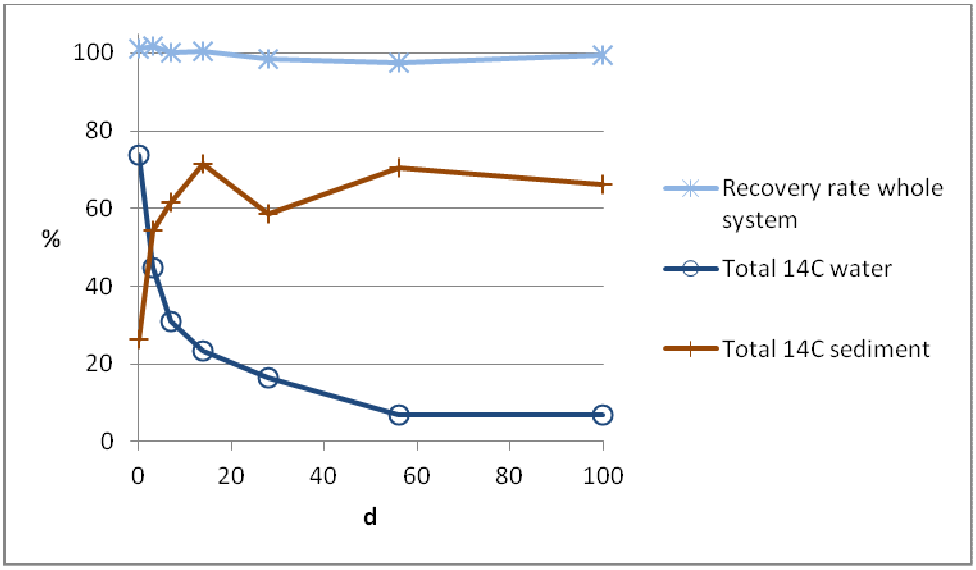


Figure 3: Recovery rate and distribution of total radioactivity in the pond system under aerobic conditions

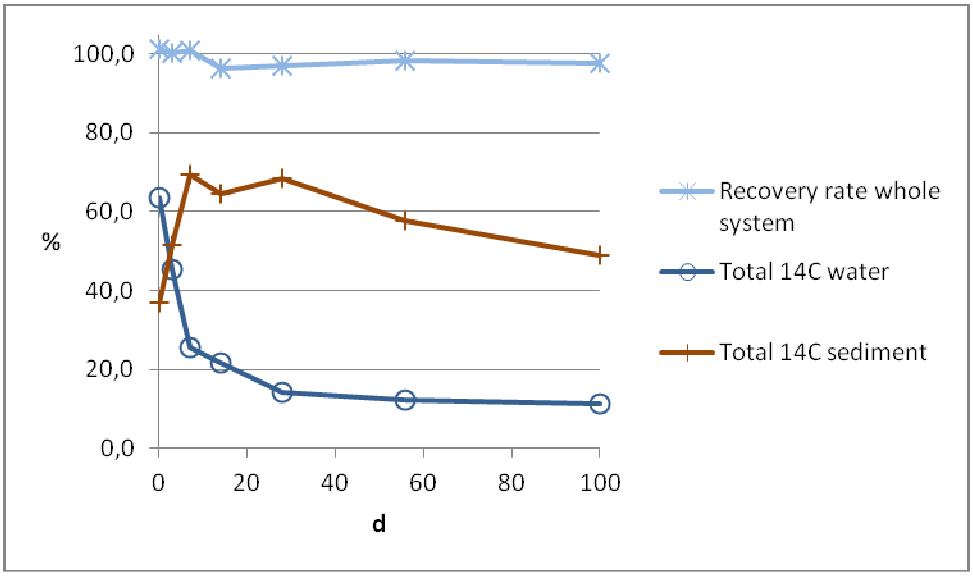


Figure 4: Recovery rate and distribution of total radioactivity in the river system under aerobic conditions

In both systems mineralisation was negligible with 1.2 or 1.3 % and the parent steadily declined to 3 or 4 % at day 100 in both systems (see Figure 5 and Figure 6). The steady decline suggests cometabolic degradation processes or abiotic degradation or dissipation processes. In neither system volatile substances were detected. One metabolite (M1, CAS 84268-36-0) was identified, only. Thus, a metabolic pathway could not be substantiated although it is clear that some degradation occurred resulting in formation of the metabolite M1.

M1**Error! Reference source not found.Error! Reference source not found.** is the respective carboxylic acid of EC 407-000-3. It was detected as the main metabolite in quantities exceeding 10 % of the applied radioactivity by far and was found as well in the water as in the sediment phase. Twelve other metabolites were detected, but not identified. Three metabolites reached amounts of 5 to 8 % each in the total system at day 100.

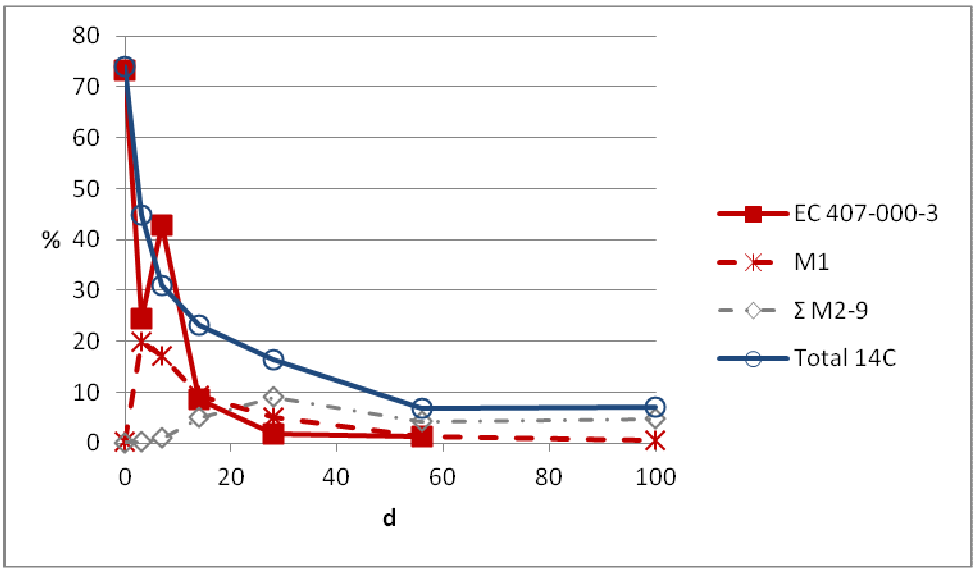


Figure 5: Parent, metabolites and total radioactivity in the water phase of the pond system under aerobic conditions

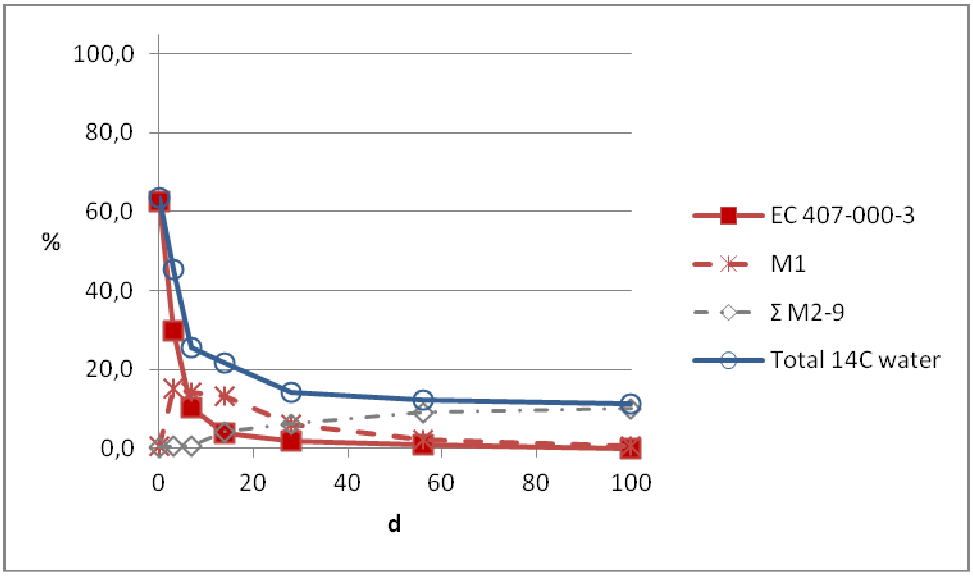


Figure 6: Parent, metabolites and total radioactivity in the water phase of the river system under aerobic conditions

The lack of mineralisation and the missing identification of further metabolites do not allow for differentiation of degradation and mere dissipation processes which contributed to the overall dissipation of M1. With no further metabolites identified adsorption and desorption of metabolites also remain unknown. Dissipation may have been caused by mere adsorption. Another aspect that hampers differentiation is the relatively high level of non extractable residues (NER), because it remains unknown to which extent parent or metabolites contributed to NER formation (see Figure 7 and Figure 8).

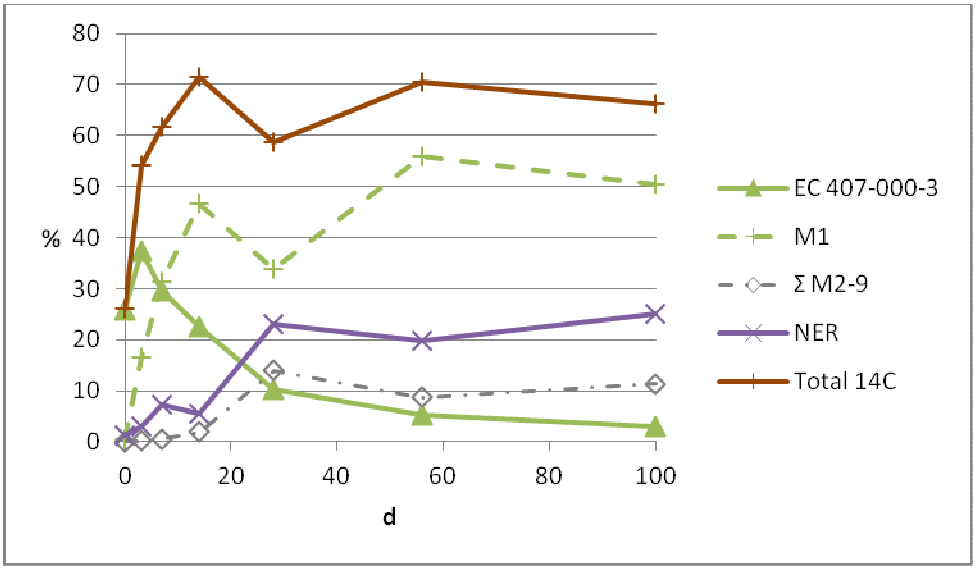


Figure 7: NER, parent, metabolites and total radioactivity in the sediment phase of the pond system under aerobic conditions

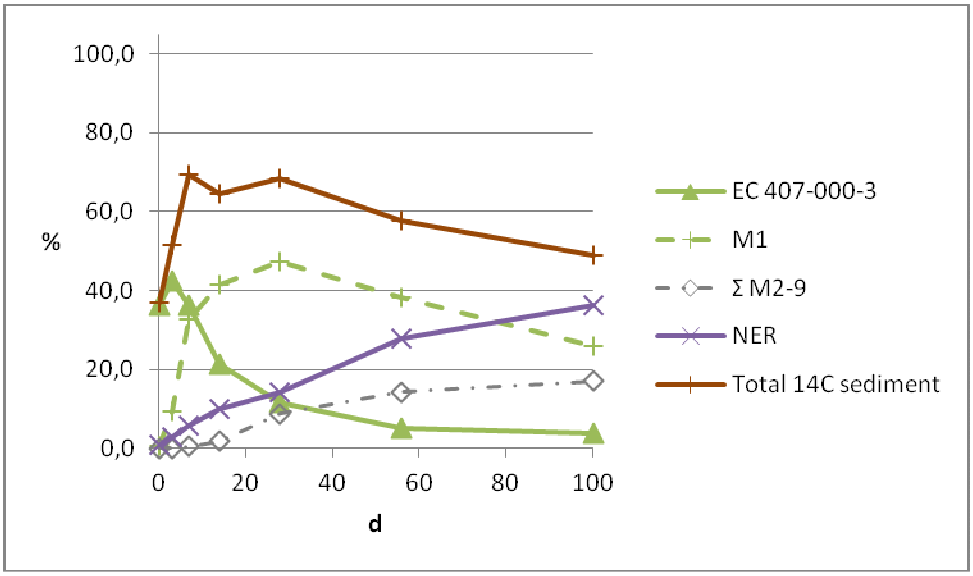


Figure 8: NER, parent, metabolites and total radioactivity in the sediment phase of the river system under aerobic conditions

In the sediment phase the trend for M1 was similar in both systems up to day 14, afterwards it differed. After reaching a maximum a clear decrease was observed in the river system, whereas only a slight decrease was observed in the pond system. In both systems the sediment values of M1 were already high at day 7 with 33 or 31 % of applied radioactivity and reached a similar high value on day 14 with 41 or 47 % (river or pond system). In the river system a maximum of approximately 47 % was reached at day 28 which finally decreased to 26 % at day 100. In the pond system an already high value of approximately 47 % on day 14 was followed by 34 % at day 28, reached a maximum of 56 % at day 56 and afterwards dropped only slightly to 50 % at test end on day 100.

In the following an attempt is made to interpret the reported concentration of M1 but it should be kept in mind that the test was not designed to follow specifically degradation of M1. Consequently data are limited and interpretation is difficult. The major uncertainty lies in the formation of further M1 from EC 407-000-3. When doing a graphical estimation of DT_{50} this leads to an overestimation of it that will depend on the amount of parent left at this point.

In both systems M1 showed similar trends in the water phase. The maximum was reached at t day 3 (15-20% overall concentration). At day 28 the concentration had dropped below 10%, i.e. half of the concentration of the maximum at day 3. An approximate DT_{50} of 25 days results. Applying a temperature correction to this leads to a DT_{50} of 55 days. According to Annex XIII a DT_{50} > 40 days would show M1 to be persistent in water provided that DT_{50} would have been a $DegT_{50}$. However, in this case dissipation from the water phase to the sediment is of major importance and is likely that the overall degradation is longer than dissipation alone, probably above 60 days.

Table 7 and Table 8 present the decline of M1 in the respective system taking the maximum value of M1 and the time at which maximum occurred as basis (see Figure 7 and Figure 8):

Table 1: Decline of M1 for sediment and whole system concentration in the river system (low org. C)

Sediment		**Whole system**	
Time in d	**Decline in %**	**Time in d**	**Decline in %**
0	0	0	0
28	20	14	2

72	46	42	27
		86	52

Table 2: Decline of M1 for sediment and whole system concentration in the pond system (high org. C)

Sediment		**Whole system**	
Time in d	**Decline in %**	**Time in d**	**Decline in %**
0	0	0	0
44	10	44	11

In the following an attempt is made to overcome the problem of a $DisT_{50}$ probably containing degradation as well as dissipation or partitioning processes by deduction of a $DegT_{50}$ from the specified $DisT_{50}$ for the purpose of comparing data with trigger values.

As stated above it is not possible to differentiate between degradation and mere dissipation processes, because of missing information on real degradation and the unknown identities of the further metabolites and thus the $DisT_{50}$ of M1 for the sediment phase represents all processes. Another aspect that hampers differentiation is the relatively high level of non extractable residues (NER), because it remains unknown to which extent parent or metabolites contributed to NER formation. NER reached 36 % in the river system and 25 % in the pond system. They were mainly bound to the humic fraction and humic acids and to a lesser part to fulvic acids. Phenolic benzotriazoles have a high log K_{OC}. Therefore they have a high tendency to adsorb.

Though data are insufficient for a detailled kinetic modelling it is possible to draw the following conclusions: $DisT_{50}$ of M1 was approximately 72 days in river system without applying temperature correction and 158 days when applying it (see Table 1 and Figure 8). This is slightly below the trigger DT_{50} < 180 days.

But as degradation shall be compared with the trigger value, these dissipation data are generally improper for comparison purposes. It can be stated though, that $DegT_{50}$ of M1 will be longer than 72 to 158 days because degradation is only one of all the processes which contribute to dissipation.

Some further aspects should be considered which contribute to the overall picture. In the pond system only 11 % dissipation of M1 was reached within 44 days. It is impossible to derive a DT_{50} for the pond system, not even a $DisT_{50}$. It may only be stated that $DisT_{50}$ > 44 days in pond system (therefore longer than 97 days when applying temperature correction). Nevertheless, a comparison with the river data (see Table 7 and Table 8) shows that dissipation in the pond system in 44 days is only about half of the dissipation measured within the river system in 28 days which means dissipation was much slower in the pond system than in the river system.

Although it is not possible to extrapolate far beyond the available time frame the pond system data show that dissipation may be very slow depending on the conditions given.

Systems with high organic content generally should be more biologically active. They also have more potential binding sites for adsorption. The latter is thought to have been the case and would explain the different dissipation half-lives between the low and the high organic content systems.

In case of unclear contribution of partition processes to dissipation and if dissipation of the substance in question mainly takes place in sediment, the whole system should be considered,

too (see Figure 9 and Figure 10). Assessing the whole system ensures that mere adsorption will not have a decisive influence on a DT_{50} because adsorbed substance will show up in sediment and thus not dissipate in whole system .

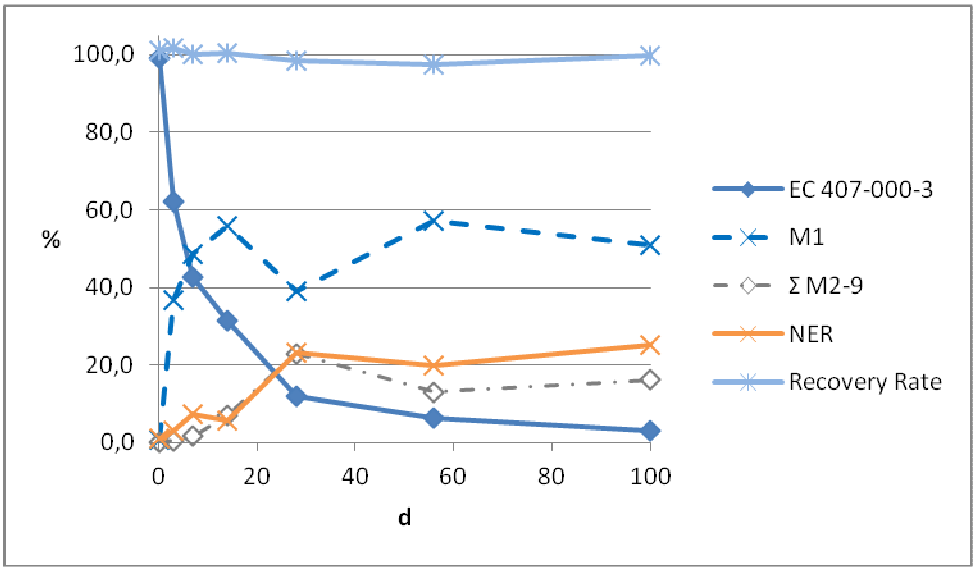


Figure 9: NER, parent, metabolites and total radioactivity in the whole system of the pond system under aerobic conditions

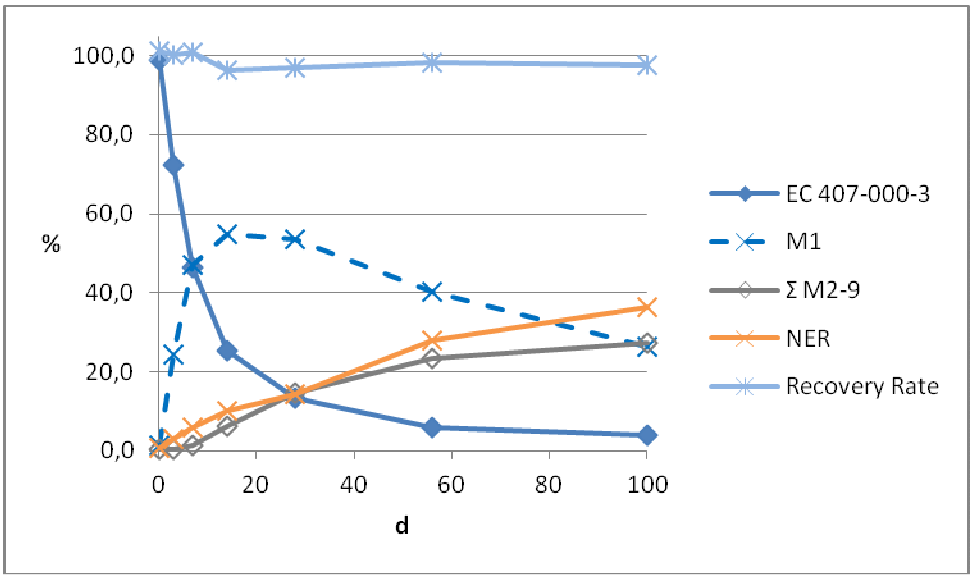


Figure 10: NER, parent, metabolites and total radioactivity in the whole system of the river system under aerobic conditions

The total occurrence of M1 (whole system) is mainly affected by M1 enrichment in sediment and consequently matches the course in sediment quite closely. Most important is the following lack of decline in the pond system (see Figure 7 to Figure 10).

In both systems the whole system values of M1 were already high at day 3, increased further and reached a similar high value on day 14. In the river system a maximum of approximately 55 % was reached at day 14 which only slightly decreased until day 28 but finally decreased to 26 % at day 100. In the pond system a near maximum of 56 % was reached at day 14, dropped afterwards to 39 % and raised again reaching finally a maximum of 57 % at day 56. It only decreased slightly to 51 % at day 100. The reason remains unclear for the decline to 39 % at day 28 in the pond system. Given the overall trend it may have been an outlier

possibly caused by problems in the extraction process. No such outlier was observed in the river system.

$DisT_{50}$ of M1 in the whole system was approximately 86 days in river system and more than 44 days in pond system. After applying temperature correction the DisT50 of the whole river system is 189 days and for the pond longer than 97 days. As degradation shall be compared with the trigger values these dissipation data are improper.

Some further aspects should be considered which contribute to the overall picture. In the pond system only 11 % dissipation was reached in 44 days (see Table 8). A comparison with the river data (see Table 7) within this time frame shows that this is only about half of the dissipation measured in the river system, i.e. dissipation was much slower in the pond system than in the river system. Moreover, dissipation may have been even much slower than this. In pond system 56 % at day 14 was observed which is as nearly as high as the maximum of 57 % at day 56 (see Figure 7). Though the reported value is slightly lower it may also have been the same at both time points if one considers measuring inaccuracy. In this case 11 % of M1 would have been dissipated in 86 days.

Even though a detailed kinetic modeling is not possible a simple worst-case kinetic estimation is possible. This estimation model considers two processes, the production of M1 from the degradation of EC 407-000-3, and the further degradation/dissipation of M1, with two complementary calculations:

A. Primary dissipation of M1 (accounting the formation from the parent)

B. Primary and secondary degradation of M1 (dissipation of M1 and identified metabolites): the ultimate degradation time of M1 will be clearly higher than this value.

The basic assumptions are:

A. EC 407-000-3 is degraded to M1, a manual fitting to the actual data is done.

B. M1 is further degraded to M2-M9. This assumption is in line with the radiolabelling of the molecule, the structure, and the finding in the different systems.

C. The modelling focuses on the last part of the experiment (the most relevant), and assumes first order kinetics for M1 allowing estimations of half-life (DT50=Ln(2)/dissipation rate)

The results for this estimation model can be inserted into Figure 9 and Figure 10 and are shown in Figure 11 and Figure 12.

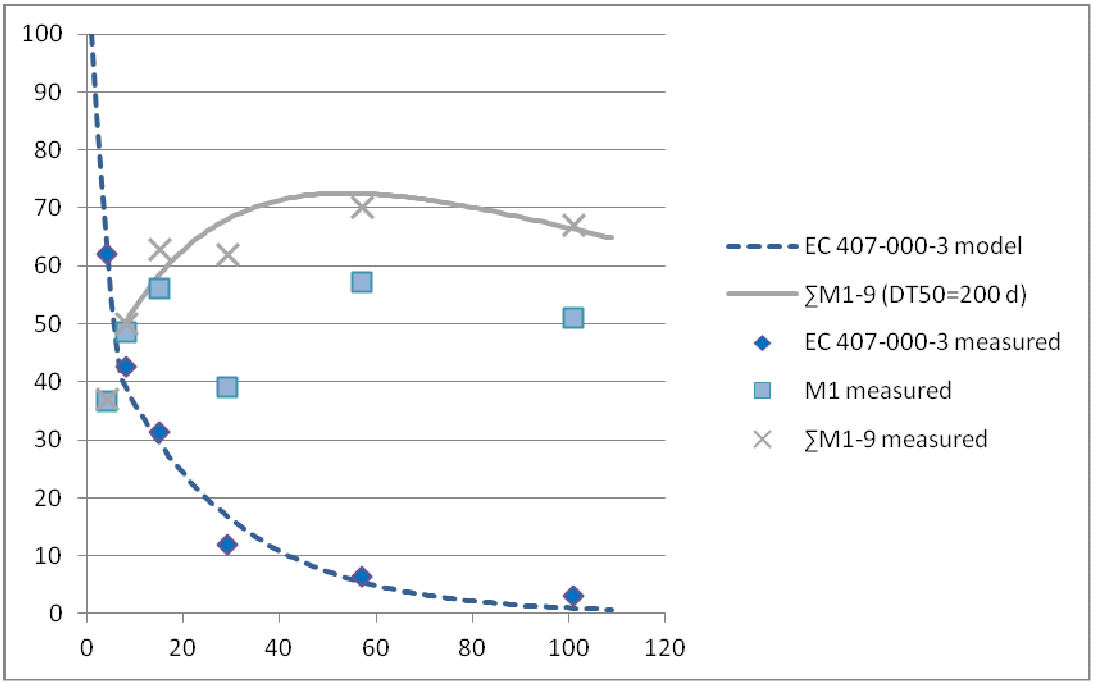


Figure 11: Parent and metabolites in the whole system of the pond system under aerobic conditions, estimation for apparent dissipation of all metabolites added (DT50 = 200 d).

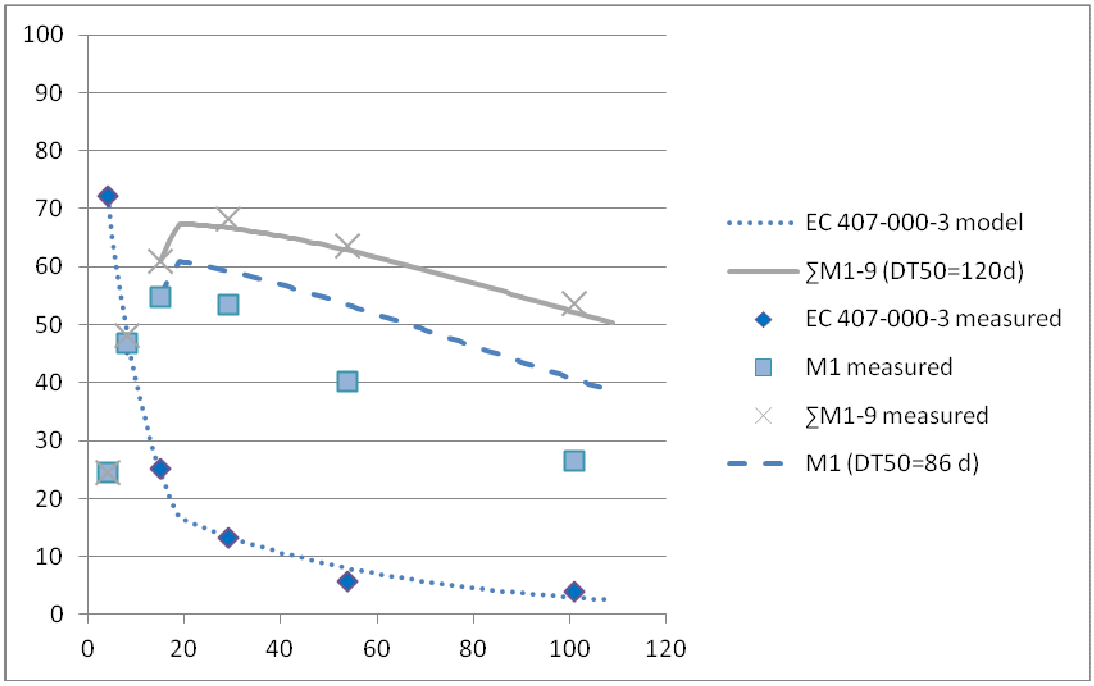


Figure 12: Parent and metabolites in the whole system of the river system under aerobic conditions, estimation for apparent dissipation of all metabolites added (DT50 = 120 d).

For both systems it is possible to model the apparent primary and secondary degradation of M1 (ΣM1-9). The estimation for the pond would lead to a DT_{50} of 200 days and for the river to a DT_{50} of 120 days. The ultimate degradation time of M1 will clearly be higher than this value. Please note also that in Figure 12 the estimation for M1 with a DT50 of 86 days is shown which overestimates the concentrations (see above).

Assessment of a a water-sediment study according to OECD 308 on EC 407-000-3 (anaerobic conditions)

A further test according to OECD 308 on degradation of EC 407-000-3 in water and sediment under anaerobic conditions was reported in the dossier on 407-000-3. Sediment was taken from an organic rich pond. In contrast to the aerobic test only small amounts of NER were found. With the exception of M1 all metabolites formed in small quantities, only.

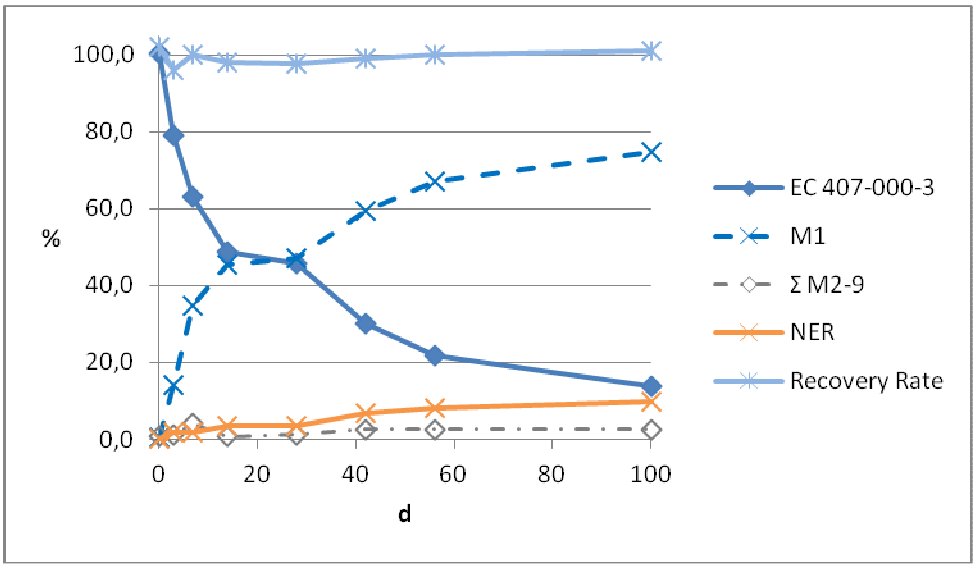


Figure 13: NER, parent, metabolites and total radioactivity in the whole system of a pond system under anaerobic conditions

M1 reached 75 % in the whole system at day 100, 65 % were located in the sediment. Up to day 14 when the maximum of 32 % was reached the majority of M1 was found in the water phase. Afterwards the concentration decreased to 10 %. In the sediment phase concentration increased to the maximum of 65 % at test end (see Figure 13).

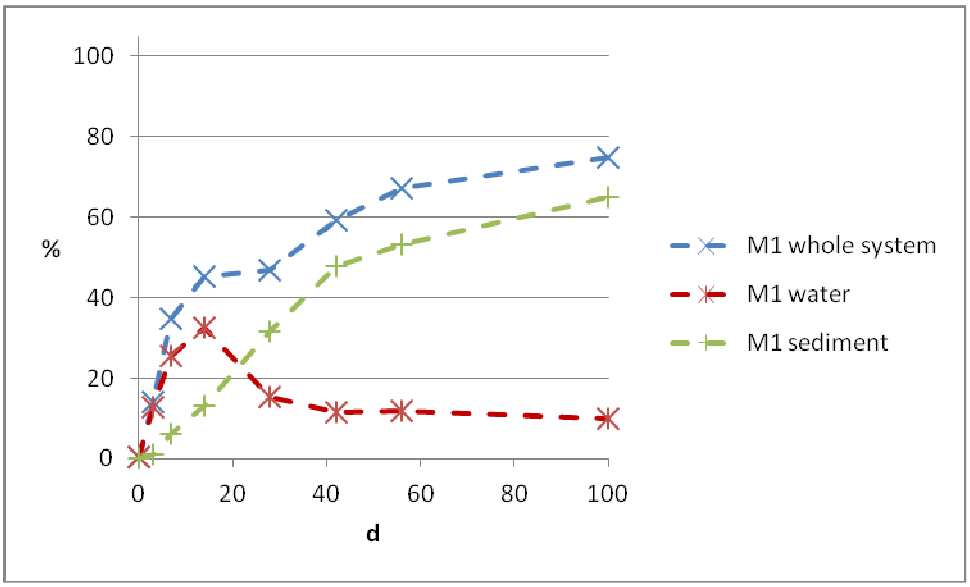


Figure 14: Main metabolite M1 in a pond system under anaerobic conditions

While EC 407-000-3 dissipated quickly its main metabolite M1 continuously built up throughout the test (see Figure 14). The test was also conducted at 20°C, therefore temperature correction would have to be employed if a $DegT_{50}$ would be calculated.

As for the aerobic systems, also for this system the degradation half life was estimated by doing a worst-case model calculation. This was based on the assumptions that all of EC 407-000-3 is degraded into M1 and this would degrade by first-order kinetics. The concentrations were calculated assuming a degradation half-life of 180 days (i.e. the vP-criterion in sediments) but not regarding temperature correction. The result is shown in Figure 15.

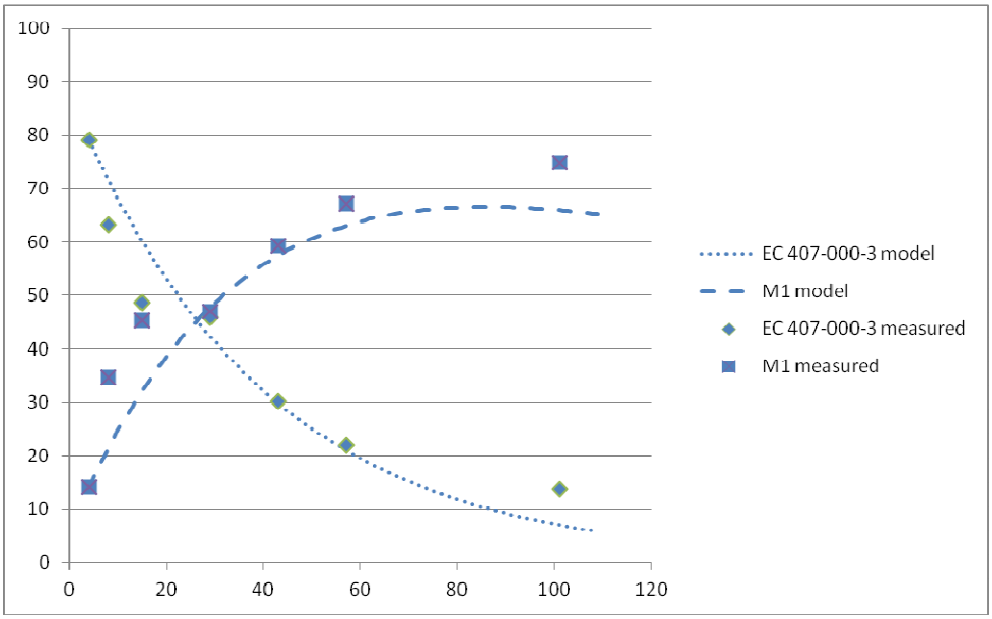


Figure 15: Model calculation on the degradation of M1 in the anaerobic system assuming a degradation half-life of 180 days (data without applying temperature correction).

The comparison of the model calculation with measured data shows that even if a DT_{50} of 180 days is assumed, the actual measured concentration of M1 is underestimated. Thus measured data indicate that at 20°C the degradation half-life is longer than 180 days.

Overall the study was not performed to determine half-lifes for the meatbolites of EC 407-000-3 and furthermore it has to be recognized that the physico-chemical properties of EC 407-000-3 and its metabolites complicate the derivation of degradation half-lifes. Nevertheless, even based on best case assumptions (i.e. favorable for degradation) it was shown that M1 will have a degradation half life of > 180 days under anaerobic conditions in sediment and in the study up to day 100 hardly any metabolites were formed and mineralization was neglectable. It is more difficult to assess the aerobic studies as under these conditions the fraction of non-extractable residues almost reaches 40% at the end of the test. Only a dissipation half life for the aerobic river system could be calclulated which was 86 days considering the whole system and 72 days considering the sediments. After applying the temperature correction this dissipation values will already be near or above the value for very perstistent substances Taking into consideration the high NER percentage and the likelyhood that dissipation does include dissipation to NER it is very likely that the overall $DegT_{50}$ will be higher. Simple kinetic modeling for the three systems at 20°C shows that the DT50 of the river system will be around 120 days, around 200 days for the aerobic pond and higher than 180 days for the anaerobic pond.

Even it can not be proven that the vP trigger is reached it has to be considered that the data show that it has to be considered that M1 does not rapidely degrade and will therefore be distributed into the anaerobic part of the sediment, where it will be even more persistent.

As M1 is a best case read-across example for the phenolic benzotriazoles in question, it was concluded that they will be also very persistent.

In the registration dossier of UV-328 simulation tests in sediment, water and soil were waived. This was explained with the physico-chemical properties of UV-328 (poor water solubility and high adsorption potential to soil and sludge), implementation of risk management measures and the results of the screening studies. In summary, the registrant assumes that the results of simulation studies would not lead to relevant different findings other than these and therefore assumes that his assessment (P and vP) would remain the same.

3.1.2.2 Biodegradation in sediments

Data from a water-sediment-test according to OECD 308 on the substance EC 407-000-3 (Dossier on 407-000-3) shows that sediment is a sink for the metabolite M1 (*cf*. 3.1.2.1.3). It is not possible to derive a $DegT_{50}$ but only a $DisT_{50}$ which is improper for comparison with the trigger values. This tentative $DisT_{50}$ is >44 days (>97 days after temperature correction) or approximately 72 days (158 days after temperature correction) depending on organic carbon content of the system for aerobic conditions. Under anaerobic conditions M1 was very persistent because it continuously built up throughout the test and a model calculation under worst case assumptions showed a degradation half life time longer than 180 days already without applying temperature correction.

3.1.2.3 Biodegradation in soil

No data available.

3.1.2.4 Summary and discussion on biodegradation

Although there are no simulation tests on UV-328 itself, the results of the screening test as

well as the result of simulation of these tests indicate a very low potential for biodegradation. The assumed degradation pathway is similar for all phenolic benzotriazoles and starts with a degradation of the side chains that are in ortho-position to the hydroxyl group of the phenolic ring. There is a simulation study on EC 407-000-3 which also gives information on a metabolite having a similar structure to the phenolic benzotriazoles in question. As it can be assumed that this phenolic benzotriazole will also be biodegraded according to the same mechanism and as it is structurally very similar to the four phenolic benzotriazoles the results of this substance can be used as an argument for read-across. As from a qualitative point of view M1 will degrade faster, this is a read-across on a best case example. Though it is impossible to compare data directly with the trigger values data give enough information to conclude that degradation will be very slow under predominant aerobic conditions in environment (based on model calculations longer than 120 days in the river system and longer than 200 days in the pond system). It is believed that adsorptive substances will reach anaerobic zones in sediment sooner or later. Therefore anaerobic biodegradation is of special interest for these substances. M1 was constantly built up under anaerobic conditions and was hardly degraded at all. The degradation process of the parent obviously stopped at this stage. A model calculation using worst case assumptions showed that the degradation half life is > 180 days. UV-328, which has also a complex aliphatic group with a quaternary carbon as side chain in its ortho-position is at least as hard to degrade and will accordingly have a degradation half-life time that is at least as long. This is supported by the simulated degradation pathway.

3.1.3 Monitoring studies

For UV-327 and UV-328 four studies are available which investigated the distribution of UV- them in sediments in a highly contaminated area (Narragansset Bay, Rhode Island, USA). Taken together, the information can be used to find some hints about the degradation potential of the phenolic benzotriazoles in sediments.

UV-327 and UV-328 were historically produced in an industrial plant at the Pawtuxet river which flows into the brackish Providence River and consequently the Narragansset Bay (Reddy et al. 2000, Junclaus et al. 1980 and Lopez-Avila and Hites, 1980). Production of UV-327 was reported between 1963 and 1972, while UV-328 was produced from 1970 to 1985 (Hartmann et al. 2005, Lopez-Avila and Hites, 1980).

Two studies provide information about the sediment concentration during the production phase:

Jungclaus et al. (Jungclaus et al., 1978) analyzed industrial WWTP effluent and receiving waters and sediments from that American specialty chemicals manufacturing plant producing organic compounds and running a badly performing WWTP. 16 water samples and 19 sediment samples (located at different sites at the Pawtuxet river including the Pawtuxet cove) were taken in 1975 and 1976 and the compounds contained were identified, beside others UV-327 and UV-328. River water and sediments were collected in Providence River and its tributary Pawtuxet River (Pruell et al., 1984). UV-328 was detected in industrial WWTP effluent (0.55 – 4.7 ppm), in river water (7 – 85 ppb) and in sediments (1-100 ppm). UV-327 was detected only in sediment, with concentrations of 2 – 300 ppm.

(Lopez-Avila and Hites, 1980) investigated the same specialty chemicals manufacturing plant located on the Pawtuxet River. Eight sediment cores were taken at three locations in the Pawtuxet River. The sites were selected for an abundance of fine-grained material. Further sediment cores were taken at four locations in the Pawtuxet Cove and 13 locations in the Providence River and Narragansett Bay. The core concentrations of the compounds in the sediment have been condensed into a single number. However, the authors feel the values given are representative of the sediment concentrations. Concentrations decrease both with

depth in the sediment and with increase in distance from the discharge.

Table 8: Concentrations of phenolic benzotriazoles in sediment cores (ppm)

	Pawtuxet River			**Pawtuxet Cove**	**Providence River**		
	near plant	**mid river**	**near dam**		**near**	**far**	**bay**
UV-327	300	400	20	80	20	2	0.5
UV-328	300	300	70	100	10	5	0.6

In summary both studies show that sediment concentrations were in the range of 2-300 ppm (UV 327), and 1-300 ppm (UV 328) in the Pawtuxet river and the providence river while concentrations in the Narragansett Bay was lower (0.5 ppm for UV 327 and 0.6 ppm for UV 328) during the actual production of these compounds.

Two further studies provide some evidence about the concentration of the compounds years after the production has ceased:

Reddy et al. (Reddy et al., 2000) examined the free and bound fractions of different substituted benzotriazoles in sediment cores from the Pawtuxet River and Narragansett Bay in the U.S. The Pawtuxet River sediment core was collected in 1989 and sectioned at 2-3 cm intervals. Eleven sections from 0-2 cm to 50-52 cm were analyzed. The sedimentation rates in this section of the river are 2-3 cm/year. The redox discontinuity, determined visually, was in the top 2 cm of the core. The Narragansett Bay core was collected in 1997. Six sections from the top 13 cm of the core were analyzed. The sediments in this area become anoxic within a few millimeters of the surface and have a sedimentation rate of about 0.3 cm/year.
The method detection limit was ca. 20 ng/g for each (free and bound) fraction.

In the Pawtuxet River core no bound benzotriazoles were detected. UV-327 was most abundant: the highest concentration was ca. 5 mg/g and it was observed down to 50-52 cm. The graph shows a varying concentration in the first 20 cm and a constant decrease with depth starting at 20-22 cm. Taking into account a sedimentation rate of 2-3 cm/year for this site, a depth of 20 cm means that exposure was 7-10 year before the actual measurement. If it is assumed that exposure was constant during the years, the decrease in the UV-327 concentration between 20 and 50 cm depth should reflect the degradation rate of UV 327. As a very rough estimate concentration decrease in depth can be compared to a decrease which would be expected assuming a DegT50 of 180 days (see Table 9, assumption: 2.5 cm depth reflects 1 year)

Table 9: Concentration profile of UV 327 based on a graphical evaluation from Reddy et al. (2000) and expected concentration based on a $DegT_{50}$ of 180 d at the different depths

Depth [cm]	**approximate measured c**	**expected c assuming a $DegT_{50}$ of 180 d [mg/kg]**
20	10^5 ng/g (100 mg/kg)	
25	4×10^3 ng/g (4 mg/kg)	25
30	6×10^2 ng/g (0.6 mg/kg)	1
40	3×10^2 ng/g (0.3 mg/kg)	0.15
52	10^2 ng/g (0.1 mg/kg)	0.075

Although this is a very rough estimation for which uncertainties need to be taken into account it supports a very slow degradation of UV-327.

In addition the study, as well as a second study by Hartmann et al (2005) can be used to compare actual concentration with historical data which also may provide some information about the degradation time (see below)

Hartmann et al. (2005) took sediment cores at three locations in Narragansett Bay in 1997 (Apponaug Cove, Seekonk River, Quonset Point). The cores were analyzed for several contaminants including UV-327 and UV-328. Two of the cores were split into 2 cm sections, and the third core (Quonset Point) was split into 10 cm sections.

The concentrations of UV-327 and and UV-328 at the different depth are summarized in table 45.

Table 10: Concentrations of phenolic benzotriazoles in sediment cores from Narragansett Bay (concentrations taken from a graph)

Quonset Point core			**Apponaug Cove core**			**Seekonk River core**	
depth [cm]	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**	**depth [cm]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**
0 – 2	ca. 40	ca. 160	0 - 2	ca. 130	ca. 270	ca. 30	ca. 120
0 – 10	ca. 60	ca. 260	2 - 4	ca. 30	ca. 80	ca. 20	ca. 70
10 - 20	ca. 80	ca. 360	6 - 8	ca. 50	ca. 140	ca. 30	ca. 140
20 - 30	ca. 100	ca. 840	10 – 12	ca. 70	ca. 120	-	-
30 - 40	ca. 130	ca. 1100	12 - 14	-	-	ca. 5	ca. 20
40 – 50	ca. 690	ca. 1180	20 – 22	n.d.	n.s.	n.d.	n.d.
50 - 60	ca. 480	ca. 40	30 – 32	n.d.	n.d.	-	-
60 - 70	n.d.	n.d.	38 – 40	-	-	n.d.	n.d.
80 - 90	n.d.	n.d.	40 – 42	n.d.	n.d.	-	-
100 - 110	n.d.	n.d.	48 - 50	-	-	n.d.	n.d.
119 - 129	n.d.	n.d.					

n.d. = not detected
- = not measured

Taking into account the specific sedimentation rate at each site, it is possible to identify the layer which probably represents exposure during active production of UV-327 and UV-328. This might be used – as a very rough estimate to compare concentrations with historical concentrations during production in order to get an idea about whether or not degradation occurred. Unfortunately historical data are not available for the three sampling site and thus the comparision is highly uncertain. However, as a second type of information the data can be used to calculate how high concentrations would have had to be during production assuming certain degradation rates. Similar calculations can be done based on the results of Reddy et al. (Reddy et al., 2000) (see above) The results of these calculations are summarized in Table 11.

Table 11: comparison of estimated historical concentrations based on a DegT50 of 180d and historical concentrations from literature

Study	**Detection limit [ng/g]**	**Site**	**Year of collection**	**Sedimentation rate [cm]**	**Layer assumed to reflect production period [cm]**	**c at that layer**	**estimated c during production (if $DegT_{50}$=180d)**	**c (historical, but probably not at the exact same spot)**
UV 327 (production period 1963 -1972								
Reddy et al., 2000	20	Pawtuxet River	1989	2-3	34 -69	10^2 ng/g (0.1 ppm) (At 52 cm)	13107 ppm	20 – 300 ppm (Junghans et al, Pawtuxet river)
Hartmann et al	10	Quonset Point (Narragansett Bay)	1997	2	54 – 68	~ 500 ng/g (0.5 ppm) (at 50 – 60 cm)	Not possible	0.5 ppm ((Lopez-Avila and Hites, 1980, Narragansett Bay)
Hartmann et al	10	Apponaug Cove (Narragansett Bay)	1997	0.5 – 0.85	14 – 29	~ 70 ng/g (0.07 ppm) (at 10 -12 cm)	Not possible	0.5 ppm ((Lopez-Avila and Hites, 1980, Narragansett Bay)
UV-328 (production period 1970 – 1985)								
Hartmann et al	10	Quonset Point	1997	2	24 – 54	~ 40 ng/g (0.04 ppm) (at 50 – 60 cm)	9175 ppm	0.6 ppm ((Lopez-Avila and Hites, 1980, Narragansett Bay)
Hartmann et al	10	Apponaug Cove	1997	0.5 – 0.85	6 - 23	~ 130 ng/g (0.13 ppm) (at 10 -12 cm)	17039 ppm	0.6 ppm ((Lopez-Avila and Hites, 1980, Narragansett Bay)

Although these data are highly uncertain they show that the assumption of a degradation half life of 180 days leads to unrealistic high starting concentrations and therefore this provides further support for the assumption that degradation of UV-327 and UV-328 in sediments is expected to be very slow, with a degradation half time above 180 days.

Sediment concentrations in the range of µg/g dw were also found in Sweden (Brorström-Lundén et al., 2011) and in heavily polluted rivers in Japan (Kameda et al., 2011). In Sweden 1.3 µg/g dw were also measured at a background site, but it was not described in more detail by the authors. Commonly, high concentrations at background sites may be interpreted as a proof of persistence. On the other hand the Swedish study is the only one with measured concentrations of that level at supposed background sites. The authors do not offer an explanation for this. It should also be noted that the detection limits for sediments were very high in the Swedish study.

There are also numerous findings of UV-328 in the environment. UV-328 was frequently investigated in monitoring studies. Studies are available from Sweden, Germany, Spain (and Portugal), USA, the Philippines, China and Japan (with certain data from other Asian countries and Poland). The substance was frequently detected in dust from houses, roads and car cabins, in soil, surface water, suspended solids, sediments, aquatic organisms, marine mammals, in WWTP influent, effluent and sludge, in storm water, landfill effluent, foodstuff and human adipose tissue. The measured concentrations show a widespread contamination of the environment over all compartments with highest concentrations in dust, (soil), sediments, biota (based on lipid weight) and WWTP sludge. Findings in the environment by themselves are no indication of persistence. Nevertheless, it is mentioned in this chapter, as the usually employed concentrations as well as overall tonnages of the phenolic benzotriazoles speak against a constant exposure with them.

3.1.4 Summary and discussion on degradation

Biodegradation is expected to be the most relevant pathway for degradation of UV-328, if there is degradation.

The overall evidence presented in chapter 3.1.2 and 3.1.3 indicate in a Weight-of-Evidence Approach that UV-328 will be persistent in the environment. This is based on the following findings:

The ready biodegradation test on UV-328 indicates a very low potential for biodegradation (2-6% after 28 days). This by itself is not enough evidence to indicate persistence but has to be seen in combination with the other available information.

The simulation study on EC 407-000-3 is used for a read-across-assessment on a best case example, namely the first metabolite of the substance which is its carboxylic acid. The study has several shortcomings for using in the assessment, most of all that it was not conducted to assess the fate of the metabolites. Also the study lasted only for 100 days, therefore, the results have to be extrapolated to compare them with the relevant trigger values for assessing persistence in sediment. Finally, the physico-chemical properties of the substance complicate matters as considerable amounts of substances are bound in non-extractable residues especially in the aerobic systems. Nevertheless it is possible to derive important information on the persistence of phenolic benzotriazoles from this test. Though it is not possible to derive half-lives for degradation from the system, for the river system where the largest amount of metabolites are found a temperature corrected $DisT_{50}$ of 189 days is found. In the anaerobic pond system the metabolite M1 is formed up to the end of the test and only small amounts of other metabolites are detected. Starting from this data it is possible to model the expected

concentrations of M1 considering a case where all of EC 407-000-3 will form M1 and this degrades by a first order kinetics. The model calculation for the data at 20°C shows that the actual half-life has to be > 180 days.

The four monitoring studies on UV-327 and UV-328 from Rhode Island show how phenolic benzotriazoles will persist in the environment. In these studies the concentrations that where found when the two substances were produced are given as well as the concentrations that were found up to 25 years later. It is not possible to derive reliable $DegT_{50}$ from these studies. Also caution is needed when comparing the data as for each study different sampling sites and methods were employed. Also, an exact description of the samples is missing (e.g. oxygen content, further contaminents, etc.). Nevertheless, from the available on one study it is possible to successfully semiquantitatevly model the concentration curve assuming slow degradation. Also, as we have some information on sampling sites and the respective sedimentation rates it is possible to assign the concentration found years after production has ceased to certain production years. With this information we can very roughly estimate the starting concentration if we assume a certain half-life. When assuming a $DegT_{50}$ of 180 days the resulting concentrations are completely unrealistic high. Therefore the $DegT_{50}$ of UV-327 and UV-328 has to be > 180 days.

Further information supports the most important findings above:

With help of UM PPS system the three complex degradation pathways for the phenolic benzotriazoles were simulated. Only one of the three will lead to complete mineralization. As the pathways are similar for the four substances as well as for the substances where a read-across is employed it is possible to generalize the individual findings and rationalize the similarities from a mechanistic point of view. The UM PPS has the drawback that it is not possible to employ quantitative kinetic models and there are also no studies known to us that prove them to be correct. Nevertheless, from the chemical point of view they predict very plausible pathways and address all possibilities.

Also, there are numerous findings in the environment in many different compartments and parts of the world. Findings in the environment are by themselves no indication for persistence as they might also be found due to constant exposure. As these substances are employed in rather small concentrations and overall tonnages it is rather unlikely that they are so frequently detected.

The assessment of the registrant of UV-328 concludes that the substance will be very persistent in the environment.

3.2 Environmental distribution

3.2.1 Adsorption/desorption

As there was no registration dossier available QSAR-based calculations were performed to estimate the adsorption behaviour to soil or suspended organic matter. Details of the prediction can be found in Annex 4. The default input parameters were used.

Table 12: Results adsorption behaviour predictions of UV-328

Model	QSAR result	Overall model performance	QPREF
EPISuite 4.1 KOW-method	K_{OC} (L/kg): 1.50 10^5 Log K_{OC}: 5.18	Reliable with Restrictions (Klimisch 2)	Annex 4.4
EPISuite 4.1 MCI-method	K_{OC} (L/kg): 4.51 10^5 Log K_{OC}: 5.65	Reliable with Restrictions (Klimisch 2)	Annex 4.4
COSMOtherm	K_{OC} (L/kg): 2.88 10^5 Log K_{OC}: 5.46	Reliable with Restrictions (Klimisch 2)	Annex 4.4

The results of the estimation of the adsorption behaviour lead to the conclusion, that UV-328 will strongly adsorb to organic material.

3.2.2 Volatilisation

The tendency for volatilization from the water phase was estimated by calculation of the Henry constant. Using the physical-chemical substance properties from Table 6, the calculated Henry constant[3] was determined to be $1.3*10^{-2}$ Pa*m³*Mol^{-1}, indicating only little tendency for volatilization. The air-water partitioning coefficient ($K_{air\text{-}water}$) may be derived from the Henry's law constant and is calculated to be $5.51*10^{-7}$ m^3/m^3. As $K_{air\text{-}water}$ and Henry's law constant are manually calculated from QSAR-based physical-chemical substance properties the reliability of the values is rated Klimisch 2.

The $K_{air\text{-}water}$ and Henry's law constant are very low suggesting that volatilisation is unlikely to be a significant removal mechanism for 2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol from aquatic systems and it is unlikely that the substance will be transported very far in the atmosphere (based on its atmospheric half-life estimated to be 8.14 hours).

3.2.3 Distribution modelling

Fugacity Level III distribution modelling

When released to the environment UV-328 will be distributed to the environmental compartments in different amount. The table below shows the result of Fugacity Level III distribution modelling using EPI Suite v4.10 with the substance properties calculated within EPI Suite. The reliability of the result from the EPI Suite calculation is rated Klimisch 2.

[3] according to equation R.16-4 from ECHA Guidance on Information requirements and Chemical Safety Assessment – Part R.16 (May 2010)

Table 13: Distribution according to Mackay Level III Fugacity Model (estimation with standard parameters as provided by EPI Suite v4.10)

compartment	**mass amount (percent)**
air	$1.53*10^{-4}$
water	3.02
soil	54.4
sediment	42.5

The results of the distribution modelling and physical-chemical substance properties lead to the conclusion that the overall amount of the substance will adsorb to the soil (54.4%) and the sediment (42.5%) when it is released to the environment.

Distribution in waste water treatment plants

The dominant route of exposure for UV-328 is expected to be wastewater which is treated in sewage treatment plants with the help of SimpleTreat. Therefore distribution modelling based on physical-chemical data from Table 14 has been conducted to estimate the distribution of the substance in sewage treatment plants. The calculation was done assuming that the substance is not readily biodegradable (k=0/h) and the reliability of the result was rated Klimisch 2.

Table 14: Distribution in sewage treatment plants (acc. to SimpleTreat 3.0, debugged version; 7 Feb 1997)

Summary of distribution	**percent**
to air	0.0
to water	8.7
via primary sludge	66.2
via surplus sludge	25.1
degraded	0.0
total	*100*

The results of the calculation leads to the conclusion, that when the substance is released into waste water the largest part of the substance will be hold back in the sewage sludge and does not enter the environment. This is in agreement with experimental findings (see Annex 6). It has to be kept in mind that the use of sludge from municipal sewage treatment plants for agricultural purposes is a common practice in many regions. Over this way the substance might be released into agricultural soil.

3.3 Bioaccumulation

When the dossier submitter compiled the Annex XV-dossier there were to his knowledge no experimental log K_{OW}-values for UV-328 available. Therefore the value was calculated with the QSAR model KOWWIN of EPISuite 4.10 and with COSMOtherm. Details on these calculations can be found in Annex 5.

Table 15: QSAR-Results for log K_{OW}-predictions of UV-328

Model	QSAR result	Overall model performance	QPREF
EPISuite 4.1 KOWWIN	Log K_{OW}: 7.25	Reliable	Annex 5.3
COSMOtherm	Log K_{OW}: 7.89	Reliable	Annex 5.3

Based on the estimated log K_{OW}-values that are larger than 4.5, it is expected that UV-328 will bioaccumulate.

Recently, UV-328 was registered. In the registration dossier of the lead registrant a log K_{OW} of >=6,5 at 23°C was found experimentally by HPLC-method. This result agrees with the QSAR-estimations.

3.3.1 Aquatic bioaccumulation

UV-328 was tested in a bioconcentration study according to OECD 305 C (NITE, 2012; reliability rated Klimisch 2). Not all test conditions can be reported because the summary of the studies does not list them. Three substance concentrations were tested in common carp (*Cyprinus carpio*). The test duration was 60 days. No information on the use of a dispersant is given, but in two similar studies on UV-327 which has also a low water solubility dispersants were used.

Table 16 lists the original report data amended with the BCF normalised to 5 % lipid content calculated with the average lipid content of start and end of test.

Table 16: BCF reported and BCF lipid normalised of UV-328 of three different test concentrations (values refer to whole body wet weight basis unless no other information is provided)

Test concentration in µg/L	$BCF_{reported}$	$BCF_{lipid\text{-}normalised}$
0.1	940[1]	1121
0.01	620 - 1800[1]	740 - 2148
0.01	2400[2]	3681

[1] Average lipid content of test fish 4.19 %

[2] Average lipid content of test fish 3.26 %

A BCF range is reported for one of the two 0.01 µg/l test concentrations. The reason for this range remains unclear and a rationale is not given. In MITI data received for other benzotriazoles (*cf.* UV-320) apparent ranges in truth represented minimum and maximum values and were given if steady state values could not be attained. It may be assumed that this holds true here, too.

Though BCF values are heterogeneous they show UV-328 to bioconcentrate. Lowest BCF values were found for the highest test concentration. This may be ascribed to test concentration being near to water solubility which frequently results in impaired accuracy of analysis. In addition overestimation of test substance concentration in water could have led to a underestimated BCF. Additional data on the study received by NITE (2012) for UV-328 show that BCF was measured separately for skin, head, innards and edibles (Table 17). Highest BCF were found in the following order: innards > head > skin > edibles.

Table 17: Reported tissue BCF

Test concentration in µg/L	**Skin**	**Head**	**Innards**	**Edible**
1.0	770, 940	1400, 1600	2300, 3600	600, 620
0.1	900, 2000	990, 2300	15000, 36000	420, 840
0.1	2300, 3100	3700, 5800	14000, 15000	1600, 1800

Furthermore, these additional data comprise depuration data. Clearance half-lives of 33, 16 and 27 days were reported for the separate test concentrations in the order as stated above.

The registration dossier of the lead registrant lists another bioconcentration study according to OECD 305 C (Ciba 2000). Documentation is generally well but some details are missing, e.g. the limit of quantification (reliability rated Klimisch 2).

UV-328 was tested at concentrations of 0.8 and 0.08 µg/L with use of solvent at 25 ± 2 °C. Substance concentration in water was measured two times a week. At each of the four sampling times 2 fish were analysed. BCF was 1120-2780 for the lower and 2300-5580 for the higher test substance concentration (see Table 15) in a flow-through system. BCF are related to whole body and wet weight. A lipid content of 4.2 % at test start is reported. Depuration half-life was 26 days for the higher and 24 days for the lower test concentration. An uptake phase of 8 weeks and an elimination phase of 56 days are reported.

Table 18: BCF reported of UV-328 at two different test concentrations (values refer to whole body wet weight basis)

Exposure time in weeks	2	4	6	8
0.8 µg/L	1270	1690	1680	2110
	1310	1120	2780	2350
0.08 µg/L	2300	3690	4400	4420
	2300	3310	5580	4760

Table 19: BCF lipid normalised of UV-328 at two different test concentrations (values refer to whole body wet weight basis)

Exposure time in weeks	2	4	6	8
0.8 µg/L	1512	2012	2000	2512
	1560	1333	3310	2798
0.08 µg/L	2738	4393	5238	5262
	2738	3940	6643	5667

Higher BCF values are found at the lower test concentration level and lower BCF at the higher test concentration level. BCF values differ approximately twofold and sometimes threefold between both test concentration levels. This effect is frequently observed for poorly water soluble substances if test concentration is overestimated or true bioavailability is lower than test concentration. This may explain the difference between both concentration levels. Consequently there is some doubt that the BCF values of the higher test concentration level

are reliable.

It remains unclear if a steady state was reached at the lower test concentration level because a third sampling time is lacking which is required to confirm this. Apart from the maximum BCF 5580 or 6643 (lipid normalised) the remaining BCF values at the sampling times 6 and 8 weeks are quite similar suggesting steady state. It is possible to calculate the average for the test end of the uptake phase after 8 weeks because difference between the samples is low. Average BCF (8 w) is 4590 for a lipid content of 4.2 % and approximately 5464 if lipid normalised to 5 %.

Nakata et al. (Nakata et al., 2010) studied occurrence of several benzotriazoles in blubber of finless porpoise (Neophocaena phocaenoides) of the Ariake Sea. They report a mean body concentration of 29 ng g^{-1} (wet weight) for UV-328 as average for 5 individuals sampled from 1998 to 2009. In the same study they also calculated the mean concentrations for UV-327 which is only 4.0 ng g^{-1} (wet wt) and leads to a BAF value of 33,300. The study has some deficiencies, e.g. a long time period over which the samples were taken. Also, only a low number of samples were available and a recalculation to whole body was necessary which is not uncommon in case of mammalian samples in monitoring studies. Some further aspects should be considered when evaluating the study. The Ariake Sea is a large bay with a maximum depth of 50 meters. Such shallow depths are preferred by finless porpoises. The bay is surrounded by several cities, e.g. Nagasaki. Therefore it is probable that there has been a steady exposition to phenolic benzotriazoles in this region in recent years. Monitoring studies confirm this assumption (*cf*. Annex6). As phenolic benzotriazoles adsorb strongly to suspended matter and sediment it is probable that the entry path into the food chain is via benthic animals taking up UV-328 from sediment. Considering nutrition behaviour of finless porpoises and its prey creates a plausible picture of transport of UV-328 through the food chain. Finless porpoises feed on small fish but also on shrimps and cephalopods, e.g. squids. Squids are carnivorous and feed on fish but also on crabs which are benthic omnivores, feeding e.g. on carrion. Shrimps feed on detritus and algae which have a large adsorption surface and are known to have weak elimination capabilities. Finless porpoises of this region also feed on sand eels (*Amodytes tobianus*) which again feed on crabs and cephalopods. Thus it is probable that finless porpoises accumulated UV-328 by food. UV-328 enriches in top predators. Considering the available data it can be assumed that the BAF value would probably be at least as high as for UV-327.

3.3.2 Terrestrial bioaccumulation

No data available.

3.3.3 Summary and discussion of bioaccumulation

In one study BCF values exceed the trigger for B for the lower test concentrations but not for the higher one. Additionally, slow clearance is reported for UV-328. UV-328 shows high bioconcentration with some BCF above the B trigger of 2000, but in this study only one of the BCF values is near to the vB-criterion. Another study also shows lower BCF values with higher test concentration but in this case the B trigger is more clearly reached in the course of the test. BCF values in the higher test concentration even reach the vB trigger and some exceed it clearly. Again, clearance is slow. Thus the available BCF-factor data for UV-328 do support the conclusion vB. The other benzotriazoles UV-320 (CAS 3846-71-7), UV-327 (CAS 3864-99-1) and UV-350 (CAS 36437-37-3) meet or exceed the vB trigger also by far. Also, enrichment at the top of the food chain has been proven in a field study for UV-328 as well as for UV-327. The data presented in thestudy suggests that UV-328 is very bioaccumulative.

Table 20 gives an overview over the available data on bioconcentration on all four phenolic

benzotriazoles discussed.

Table 20: Overview of the available data on bioconcentration properties of UV-320, UV-327, UV-328 and UV-350 (values refer to whole body wet weight basis unless no other information is provided)

Substance	Species	BCF/BAF (lipid norm.)	c [µg/L]	Test system	Type	References
UV-320	*Cyprinus carpio*	1,945*	10	OECD 305C	kinetic	(NITE, 2012)
		5,905*	1			
		12,041*	0.1			
UV-327	*Cyprinus carpio*	1,203	1.0	OECD 305C	steady state	(NITE, 2012)
		6,283	0.1			
		8,817	0.1			
		7,540	0.01			
	Neophocaena phocaenoides	5,946	0.012 **	Monitoring	-	(Nakata et al, 2010)
UV-328	*Cyprinus carpio*	1,121	0.1	OECD 305C	steady state	(NITE, 2012)
		740-2,148	0.01			
		3,681	0.01			
	Cyprinus carpio	*1333-3309*	0.8	OECD 305C	-	(CIBA, 2000)
		2738-6650	0.08			
UV-350	*Cyprinus carpio*	20,263	1.0	OECD 305C	steady state	(NITE, 2012)
		34,210	0.1			

* at test end

** geometric mean concentration reported by Ministry of Environment, Japan

Based on the the determined BCF value of 5464 in the study conducted by CIBA (2000), it was concluded that UV-328 is very bioaccumulative. This is in line with the findings of the three similar phenolic benzotriazoles.

The bioaccumlative characteristics of UV-328 are supported by numerous findings of UV-328 in aquatic biota in monitoring studies. In marine fish and marine tidal flat organisms concentrations up to several hundred ng/g lw were found (Kim et al., 2011 b and c; Nakata et al., 2009a). In mussels such high concentrations were found regularly (Nakata, 2011, Nakata et al., 2012). Concentrations were lower, but still regularly found in marine shallow water organisms (Nakata et al., 2009a) and in human adipose tissue (Yanagimoto et al., 2011). UV-328 is accumulated in the blubber of marine mammals and an increasing temporal trend is stated for marine mammals in Japan (Nakata, 2011). In summary monitoring data on UV-328 can give a certain indication that bioaccumulation may occur.

3.4 Secondary poisoning

UV-327 and UV-328 enrich in top predators (*cf*. (Nakata et al., 2010)).. Though no direct proof was given in the study itself the habitat may be assumed as having been continuously exposed to phenolic benzotriazoles and such has been the prey. Several biomonitoring studies suggest

that as well (see Annex 6). Moreover, adsorptivity of UV-328 and information on the diet of finless porpoise and its prey show a plausible and very probable transport of the substance through the food chain. Thus it is concluded that UV-328 accumulates through the food chain. This is supported to some extent by the appearance of the substance in foodstuff and (in higher concentrations) in human adipose tissue (Yanagimoto et al., 2011). However, uptake by humans could also take place via air, dust etc.

4 Human health hazard assessment

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.2 Acute toxicity

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.3 Irritation

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.4 Corrosivity

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.5 Sensitisation

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.6 Repeated dose toxicity

4.6.1 Non-human information

4.6.1.1 Repeated dose toxicity: oral

There is evidence based on the RAC opinion on UV-328 (see Annex 8) that the substance meets the criteria for classification as specific target organ toxic after repeated dose cat.2 (STOT RE 2).

4.7 Mutagenicity

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and

57 (e).

4.8 Carcinogenicity

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.9 Toxicity for reproduction

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

4.10 Other effects

5 Environmental hazard assessment

5.1 Aquatic compartment (including sediment)

5.1.1 Toxicity data

5.1.1.1 Fish

5.1.1.1.1 Short-term toxicity to fish

In 2007 a study was presented under the Existing Chemicals Law of Japan were in a 96 h acute toxicity test a LC_{50} of >5.00 mg l^{-1} was reported. In an OECD Testing Guideline 203 study conducted on the same species a LC_{50} larger than 0.078 mg l^{-1} was reported, meaning that no effect was observed until the water solubility limit was reached. No further information on test conditions can be provided. The tests seem to be conducted according to standard guidelines, only a summary was checked.

Table 21: Acute toxicity of UV-328 on fish

Species	Duration	LC_{50} (mg l^{-1})	Method, conditions	Reliability	Reference
Oryzias latipes	96h	>0.078	OECD TG 203	Klimisch 4	(Japan, 2006)
Oryzias latipes	96h	>5.00	Japanese Industrial Standard (JIS K 0102-1998-71)	Klimisch 4	(Japan, 2006)

5.1.1.1.2 Long-term toxicity to fish

No data relevant for assessing the T-criterion can be reported.

5.1.1.2 Aquatic invertebrates

5.1.1.2.1 Short-term toxicity to aquatic invertebrates

An OECD 202 study on *Daphnia Magna* was conducted in 2006 for the Japan Challenge Program. The summary of the study result can be found in the Japan CHEmicals Collaborative Knowledge database. According to the study the LC_{50} was larger than 0.083 mg l^{-1} (Japan, 2006). The reliability of this study was rated Klimisch 4, because only a summary of the study was available.

There is also a recent study by Kim et al. testing the acute toxicity of the Benzotriazole based UV-stabilizers UV-9, UV-234, UV-320, UV-326, UV-327, UV-328, UV-329, UV-360 and UV-571. The tests were also conducted according to the OECD Testing Guideline 202 on *Daphnia Pulex* at concentrations 0.1, 0.5, 1.0, 5.0 and 10.0 mg l^{-1} (Kim et al., 2011a). Only for UV-571 acute toxic effects were reported with an LC_{50}(24h) of 6.35 mg l^{-1} and an LC_{50}(48 h) of 2.59 mg l^{-1}. For all the other stabilizers no toxic effects were observed under the concentrations tested in the study.

Table 22: Short-term-toxicity of UV-328 on aquatic invertebrates

Species	Duration	EC_{50} (mg l^{-1})	Method, conditions	Reliability	Reference
Daphnia Magna	48 h	>0.083	OECD TG 202 (Acute immobilization)	Klimisch 4	(Japan, 2006)
Daphnia Pulex	24 h	>10	OECD TG 202	Klimisch 1	(Kim et al., 2011a)
Daphnia Pulex	48 h	>10	OECD TG 202	Klimisch 1	(Kim et al., 2011a)

5.1.1.2.2 Long-term toxicity to aquatic invertebrates

No data relevant for assessing the T-criterion can be reported.

5.1.1.3 Algae and aquatic plants

An OECD 202 study on *Pseudokirchneriella subcapita* was conducted in 2006 for the Japan Challenge Program. The summary of the study result can be found in the Japan CHEmicals Collaborative Knowledge database. A NOEC of 0.016 mg l^{-1} for growth inhibition was reported. This is the most sensitive endpoint of all acute toxicity studies on UV-328 known to us (Japan, 2006). The reliability of this study was rated Klimisch 4, because only a summary of the study was available.

Table 23: Toxicity of UV-328 on algae

Species	Duration	EC_{50} (mg l^{-1})	NOEC (mg l^{-1})	Method, conditions	Reliability	Reference
Pseudokirchneriella subcapita	72 h	>0.016	0.016	OECD TG 201 (growth inhibition, velocity method)	Klimisch 4	(Japan, 2006)

5.1.1.4 Sediment organisms

No data relevant for assessing the T-criterion can be reported.

5.1.1.5 Other aquatic organisms

No data relevant for assessing the T-criterion can be reported.

5.2 Terrestrial compartment

No data relevant for assessing the T-criterion can be reported.

5.3 Atmospheric compartment

No data relevant for assessing the T-criterion can be reported.

5.4 Microbiological activity in sewage treatment systems

No data relevant for assessing the T-criterion can be reported.

5.5 Non compartment specific effects relevant for the food chain (secondary poisoning)

No data relevant for assessing the T-criterion can be reported.

5.5.1 Toxicity to birds

No data relevant for assessing the T-criterion can be reported.

5.5.2 Toxicity to mammals

See Chapter 4.6

5.6 Toxicity test results concerning endocrine disruption relevant for the environment

As there is some discussion on endocrine disrupting properties data on this issue was compiled in Annex 7.

6 Conclusions on the SVHC Properties

6.1 PBT, vPvB assessment

6.1.1 Assessment of PBT/vPvB properties – comparison with the criteria of Annex XIII

6.1.1.1 Persistence

If UV-328 is degraded, biodegradation is expected to be the most relevant pathway for degradation.

There are no degradation simulation tests on UV-320 itself. Nevertheless Annex XIII allows conclusions on the persistence according to REACH Annex XIII 2. REACH Annex XIII 2 in turn allows the assessment of PBT-properties in a weight-of-evidence approach, as defined in REACH Annex XI 1.2. This means that information from several independent sources is considered to conclude on a dangerous property, in this case the persistence. While each single source of information might be regarded as insufficient to support the conclusion, the combined information is, due to its weight of evidence, regarded to be sufficient.

In case of UV-328 the weight-of-evidence-approach is based on the following important facts:

- The results of the screening test as well as the result of simulation of this tests indicate a very low potential for biodegradation
- There is a simulation study on a very similar phenolic benzotriazole that available allows a read-across assessment: While the study on EC 407-000-3, a similar substance which should degrade faster, does not allow a direct comparison of data with the trigger values, it shows that even dissipation of its first metabolite is very slow ($DisT_{50}$ of 86 days in a river system at 20°C, 189 days when temperature corrected for 12°C). Thus degradation will be even slower. This metabolite is hardly degraded at all under anaerobic conditions and the degradation half-life for this is > 180 days even at 20°C. Considering the high potential for adsorption these conditions are expected to be of special importance and anaerobic soil and sediments are expected to be substance sinks, as the substance does not rapidly degrade.
- There is a case of several studies on deeper sediments on Rhodes Island, where UV-327 and UV-328 are found in sediments up to 25 years after the production of the substances in a nearby chemical plant has stopped. Estimations on concentration curves indicate that the DegT50 has to be larger than 180 days to explain the findings.

Furthermore there is additional data supporting this assessment:

- Once released into the environment most UV-328 will be bound to soil and sediment as the substance has a very high potential for adsorption. This was demonstrated by experimental results on sewage sludge as well as simulated log K_{OC} values.
- In the common relevant mechanism for degradation of phenolic benzotriazoles the side-chain in ortho-position is degraded. The more complex this side chain is, the longer it will take for the respective substance to be degraded. In case of UV-328 a tert-pentyl group has to be degraded.
- In many environmental monitoring studies UV-328 was analysed. It was detected in a variety of different compartments in some regions of the world (see Annex 6).

In conclusion it was assessed considering the weight-of-evidence approach that UV-328 must be considered to be very persistent in the environment and meets the P and the vP criteria of REACH Annex XIII.

The assessment of the persistence of UV-328 in the registration dossier was based on the screening tests and also resulted in assessing the substance as having P and vP. Simulation tests in water, sediment and soil were waived.

6.1.1.2 Bioaccumulation

The BCF-values of all other benzotriazoles considered meet the vB-criterion and thus, the read-across to these structurally similar substances suggests that UV-328 meets the vB-criterion, too (see Table 20). The available experimental BCF values of UV-328 with the highest value of 5464 support this. Relevant monitoring data are available and elevated levels in biota were detected by Nakata et al. (Nakata et al., 2010). This demonstrates that UV-328 accumulates through the food chain and enriches in top predators. Thus it was concluded that based on all available information UV-328 is very bio accumulative and meets the B and the vB criterion according to REACH Annex XIII.

6.1.1.3 Toxicity

On 11 June 2013 RAC adopted the opinion (Annex VIII) that UV-328 meets the criteria as STOT RE 2 as defined in the CLP regulation (EC) 1272/2008. Therefore UV-328 has to be considered as toxic.

6.1.2 Summary and overall conclusions on the PBT, vPvB properties

According to a weight-of-Ewvidence argumentation UV-328 has to be considered vP and therefore also P.

Overview of the conclusions of the weight-of-evidence approach:

- ready biodegradation tests of UV-328 indicates a very low potential for biodegradation (2-6% after 28 days);
- Read-across assessment on EC 407-000-3 and its first metabolite: Very slow dissipation in aerobic systems (sediment and water) near or above the vP-trigger value based on data for the different compartments with and without temperature correction. Modelling of anaerobic system shows a DegT50 > 180 days already at 20°C. Degradation of the substances in question has to be even longer;
- For UV-327 and UV-328 there are monitoring studies available showing that the substances were found decades after environmental exposure has stopped. Model calculations indicate that these findings can only be explained if the $DegT_{50}$ is larger 180 days.
- Further supporting information:
    - Simulation of the complex degradation pathways gives a mechanistic explanation for similarities and findings;
    - Numerous findings in the environment in many different compartments and parts of the world although substances are used in small concentrations and overall tonnages are low.

Thus, applying the weight-of-evidence approach the substance fulfills the P and the vP-criterion of REACH Annex XIII

Also, based on the BCF study by CIBA (2010) and in light of all available data (e.g. Nakata et al. 2010) the substance fulfils the criterion to be considered vB. Finally, UV-328 fulfils also the criteria to be classified as STOT-RE 2 and therefore can be considered as toxic. In conclusion UV-328 has vPvB- and PBT-properties.

6.2 CMR assessment

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (d) and 57 (e).

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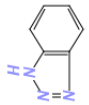
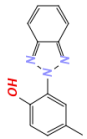
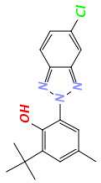
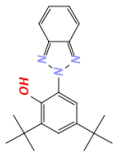
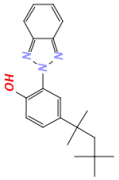
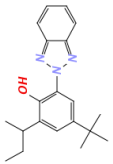
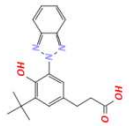
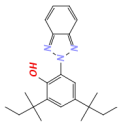
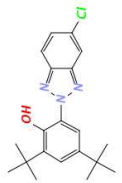
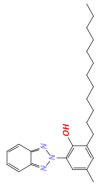
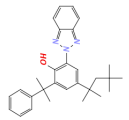
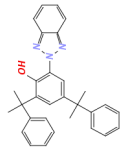
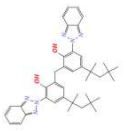
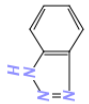
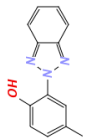
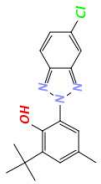
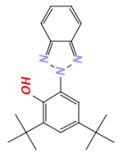
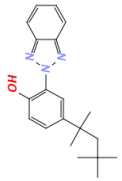
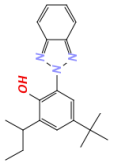
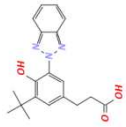
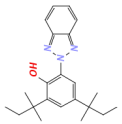
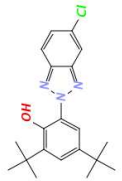
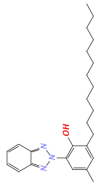
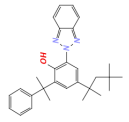
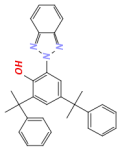
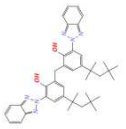
ANNEX 1: Read-Across-Data-Matrix

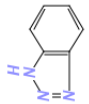
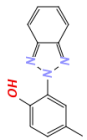
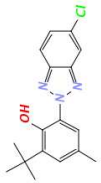
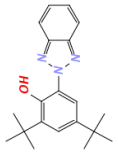
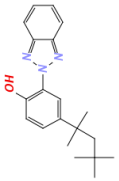
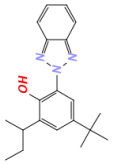
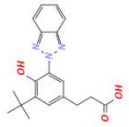
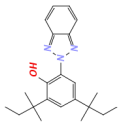
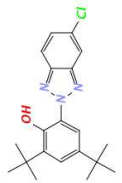
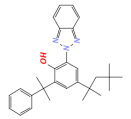
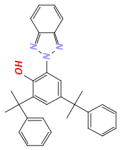
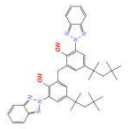
In this matrix all available experimental results that might be relevant for the SVHC-identification are listed for all four substances in questions as well as all other substances mentioned in the dossier or used for a Read Across. The substances are ordered in order of rising molecular weight.
QSAR results were intentionally left out in this overview. In cases where several data points were available the most reliable one is presented and in cases where a decisions was not possible (as is for example the case for registration data disseminated on ECHAs webpage) all data point are presented.

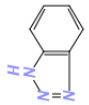
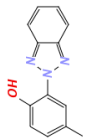
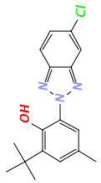
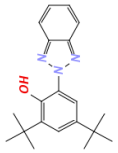
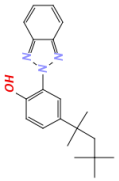
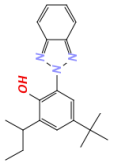
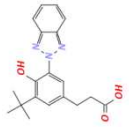
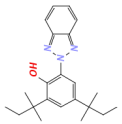
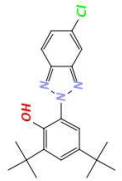
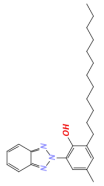
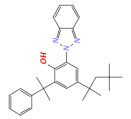
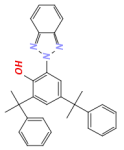
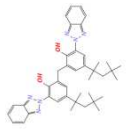
Acronym	**1H-Benzotriazole**	**UV-P**	**UV-326**	**UV-320**	**UV-329**	**UV-350**	**M1[4]**	**UV-328**	**UV-327**	**UV-571**	**UV-928**	**UV-234**	**UV-360**
													
CAS No	95-14-7	2440-22-4	3896-11-5	3846-71-7	3147-75-9	36437-37-3	84268-36-0	25973-55-1	3864-99-1	125304-04-3	73936-91-1	70321-86-7	103597-45-1
EC No	202-394-1	219-470-5	223-445-4	223-346-6	221-573-5	253-037-1	-	247-384-8	223-383-8	-	422-600-5	274-570-6	403-800-1
Physicochemical Data													
Mol. Weight [g/mol]	119.1	225.3	315.8	323.4	323.4	323.4	339.4	351.5	357.9	393.6	441.6	447.6	658.9
log Kow	1.44[5]	4.31[5] 4.2[7]						>6,5[6]				>6.5[7]	4.2[8]; 12.7[8,9]
pK_A	8.37[10]												

[4] Degradation Product of EC 407-000-3
[5] Hansch, C. et al: Exploring QSAR Vol 2: Hydrophobic, Electronic, and Steric Constants (1995)
[6] Registration dossier of the lead registrant
[7] The Phenolic Benzotriazoles Association: HPV Challenge Program, Data Summary and Test Plan for Phenoluic Benzotriazoles (2001)
[8] Data disseminated on ECHA-Homepage
[9] This value is so large that is probably not reliable
[10] Serjeant,EP & Dempsey,B: Ionisation constants of organic acids in aqueous solution, p. 159 (1979)

Acronym	1H-Benzotriazole	UV-P	UV-326	UV-320	UV-329	UV-350	M1[4]	UV-328	UV-327	UV-571	UV-928	UV-234	UV-360
													
log Koc													5.63[8]
Water sol. [mg/L]	19800[11]	0.173[12]; 0.8[13]			<1[7]			0.015[13] < 0,001 (at 20°C)[6]	0.022[13]			<0.04 (at 20°)[7]	<0.007[8]
Vapor pressure [Pa]								0,000005 (at 20°C)[6]					6 10^{-13} [8]
Data on Degradation													
ready biodegradability screening tests	non-biodegradable MITI-1 (OECD TG 301C), BOD =2[14]	Not readily biodegradable (OECD TG 301 B), 0–2% after 28 days[12]		non-biodegradable MITI-1 (OECD TG 301C), BOD =0[14]	Not readily biodegradable (OECD TG 301 B), 0–1% after 28 days[12]			Not readily biodegradable (OECD TG 301 B), 2–8% after 28 days[12]	non-biodegradable MITI-1 (OECD TG 301C), BOD =0[14]		Not readily biodegradable (OECD TG 301 B), -4–3% after 28 days[15]	Not readily biodegradable (OECD TG 301 B), 3–8% after 28 days[12]	Biodegradation in water <10% (84/499/CEE method 5) [8]; Biodegradation in water <2% (84/499/CEE

[11] Davis, LN et al: Investigation of selected potential environmental contaminants: benzotriazoles, USEPA-560/2-77-001 (1977)
[12] US EPA Screening-LevelHazard Characterization Sponsored Chemicals Phenolic Benzotriazoles Category (2009)
[13] Lopez-Avila, V & Hites, RA: EnvSciTechnol 11, p. 1382-1390 (1980)
[14] Biodegradation and Bioconcentration Database of the Existing Chemical Substances; available: http://www.safe.nite.go.jp/jcheck/english/search.action
[15] Australia: Nantional Industrial Chemicals Notification and Assesment Scheme - Full Public Report - Tinuvin 928 (2000)

Acronym	1H-Benzotriazole	UV-P	UV-326	UV-320	UV-329	UV-350	M1[4]	UV-328	UV-327	UV-571	UV-928	UV-234	UV-360
													
													method 5) [8]; Biodegradation in water 0% (84/499/CEE method 5) [8]
Simulation tests	Primary degradation aerobic: DT_{50}=114 d anaerobic: DT_{50}=144 d						OECD 308 aerobic: $DisT_{50}$ = 86 d (river system) $DisT_{11}$ = 44 d (pond system) anaerobic: build up until test was ended (100 d)						
Data on Bioaccumulation													
BCF (lipid	1000 µg/L: 1-	1000 µg/L:	500 µg/L:	10 µg/L: 1945;		**1 µg/L: 20263;**		0.1 µg/L: 1121;	1 µg/L: 1203;				

Acronym	1H-Benzotriazole	UV-P	UV-326	UV-320	UV-329	UV-350	M1[4]	UV-328	UV-327	UV-571	UV-928	UV-234	UV-360
													
normalized) acc. To OECD 305 C on Cyprinus carpio	3; 100 µg/L: 5-17[14]	171-686; 100 µg/L: 181-410; 10 µg/L: 55-275[14]	71-143; 50 µg/L: 258-1055; 5 µg/L: 721-1178[14]	**1µg/L: 5905; 0.1 µg/L: 12041[14]**		**0.1 µg/L: 34210[14]**		0.01 µg/L: 740-2148; 0.01 µg/L: 3681[14] 0,8 µg/L: 2655; **0,08 µg/L: 5464**[6]	**0.1µg/L: 6283/8817; 0.01 µg/L: 7540[14]**				
Field BAF calculated based on Nakata et al 2010 on Neophocaena phocaenoides									**0.012 µg/L: 5946[16]**				

[16] : Nakata H et al.: Detection of benzotriazole UV stabilizers in the blubber of marine mammals by gas chromatography-high resolution mass spectrometry (GC-HRMS). J Environ Monit 12, p. 2088-2092 (2010)

Annex 2: Overview of Self-Classifications

Table 24: Self Classifications for UV-328 according to Regulation (EC) 1272/2008 (CLP)

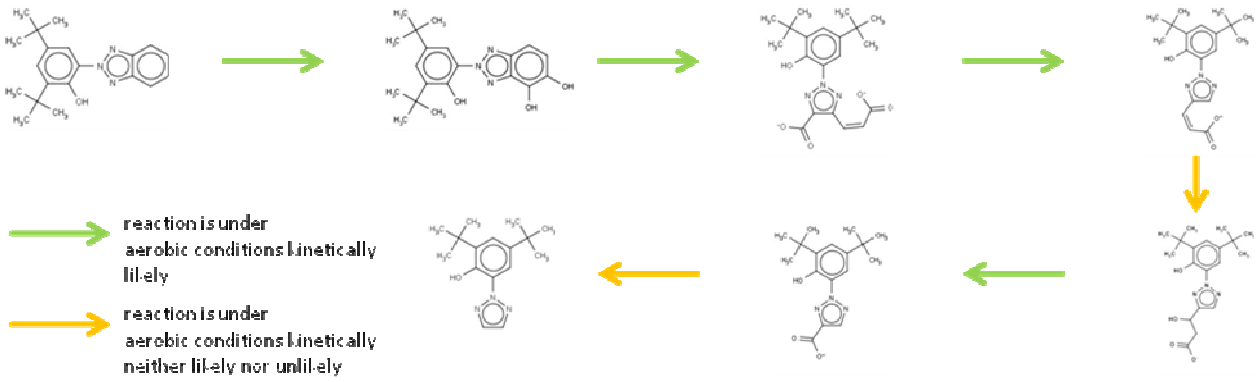
Name / Tradename	EC-number	Hazard Class and Category Code(s)	Hazard Statement Code(s)
2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol UV-328	247-384-8	Acute Tox. 2 Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 4 Resp. Sens. 1 STOT SE 3 STOT RE 1 STOT RE 2 Aquatic Chronic 2 Aquatic Chronic 3 Aquatic Chronic 4	H302 H312 H315 H319 H332 H334 H335 H372 H373 H411 H412 H413

ANNEX 3: Overview of the simulated degradation pathways for UV-320, UV-327, UV-328, UV-350, EC 407-000-3 and 1H-Benzotriazole as predicted by the UM-PPS

Please note that all possible reaction pathways are idealized, i.e. they do not include side reactions.

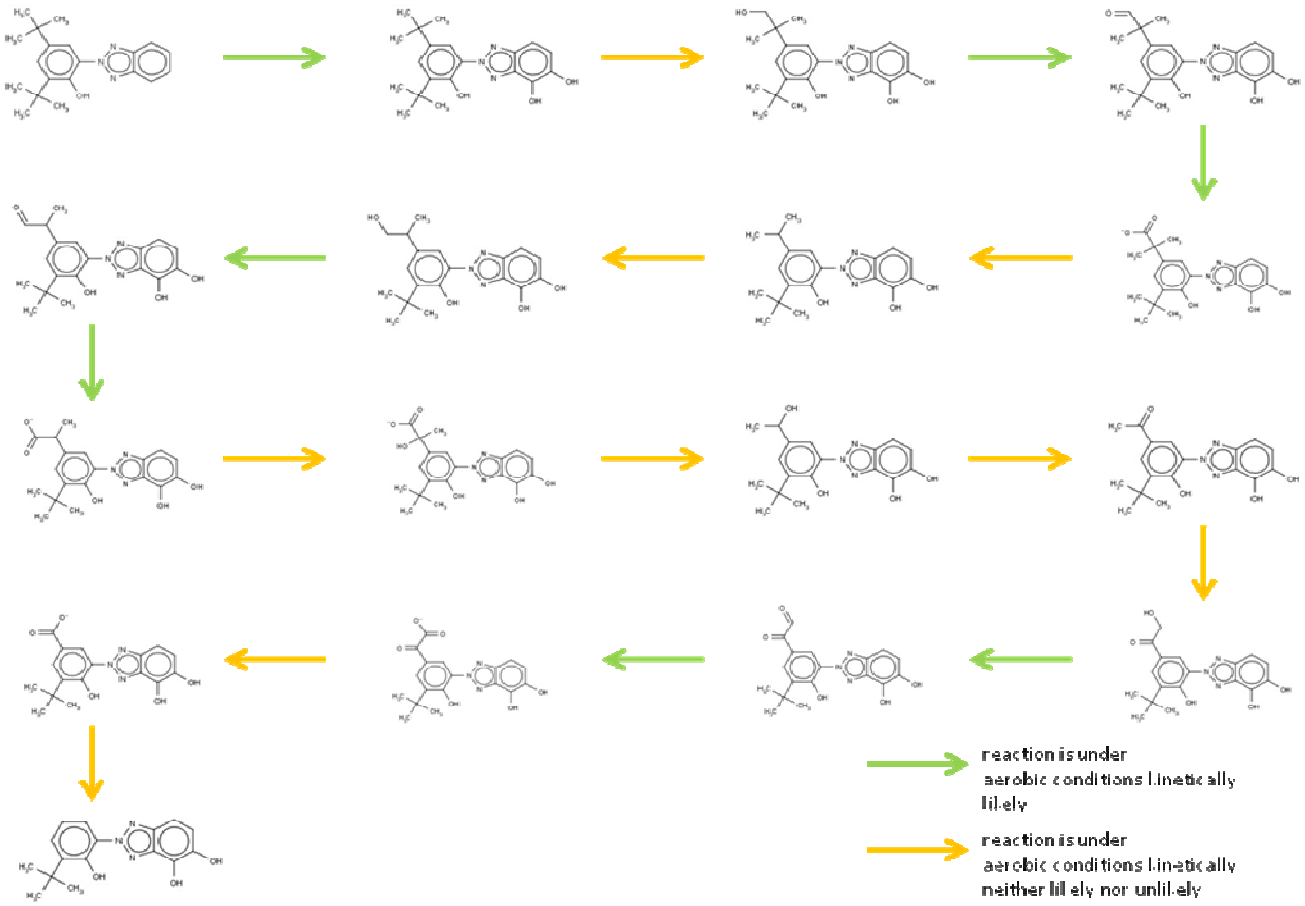
UV-320:

a) Degradation of the benzotriazole moiety



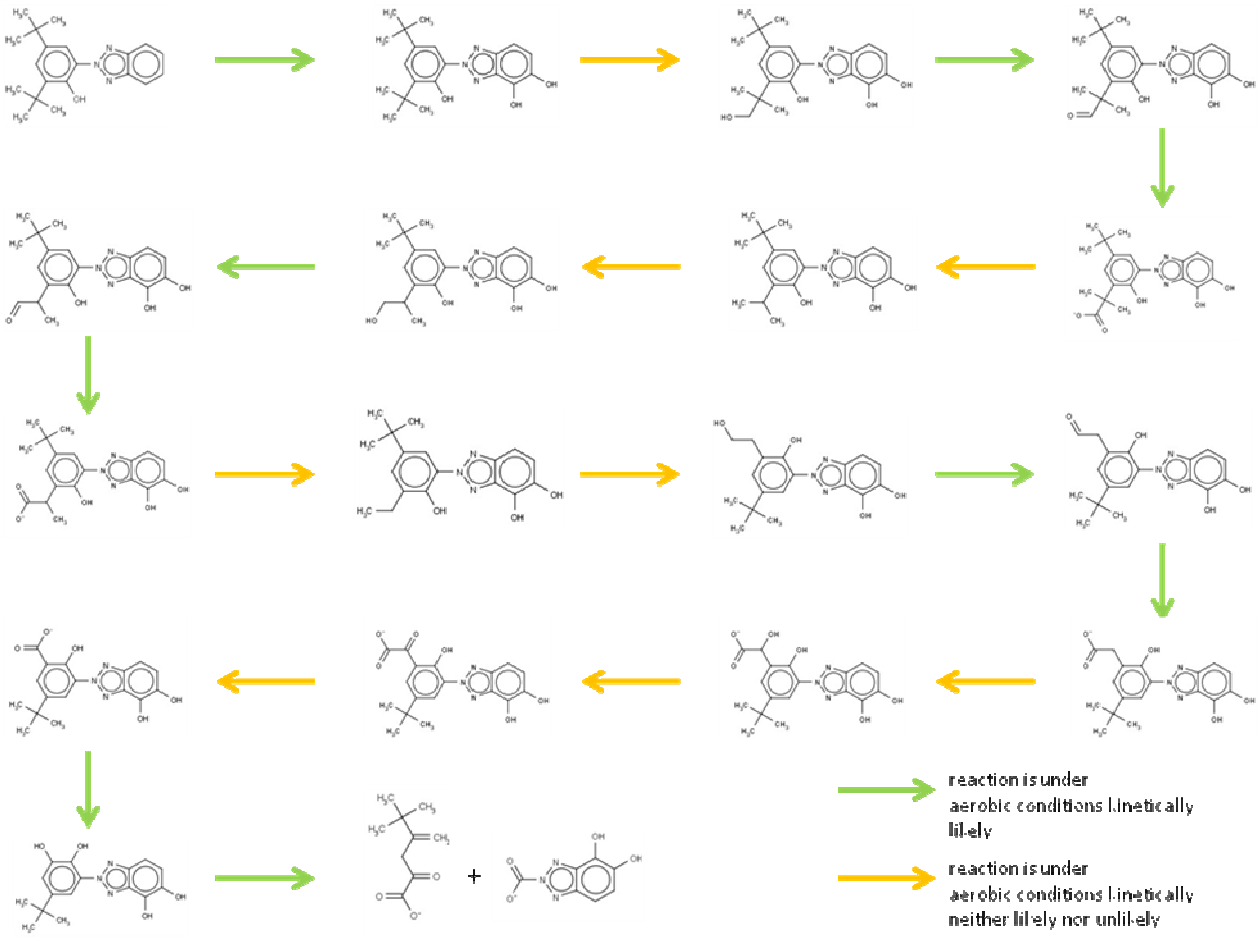
This reaction is possible for all phenolic benzotriazoles but is not shown for UV-328, UV-350 and EC 407-000-3 as it would be redundant.

b) Degradation of tert-butyl side-chain in para-position to the hydroxyl group



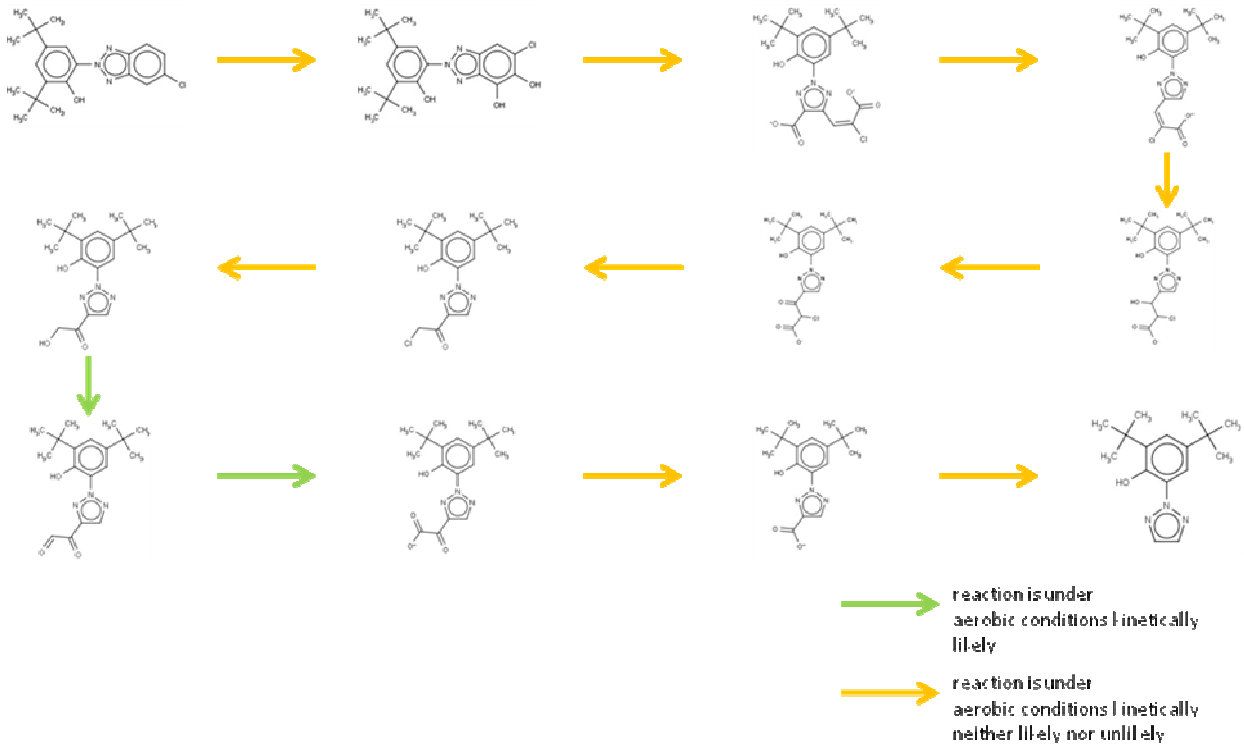
This reaction is also possible for UV-327 and UV-350 but is not shown for these molecules as this would be redundant. All three molecules are substituted with a tert-butyl group in para-position to the hydroxyl group.

c) Degradation of the tert-butyl side-chain in ortho-position to the hydroxyl group



UV-327:

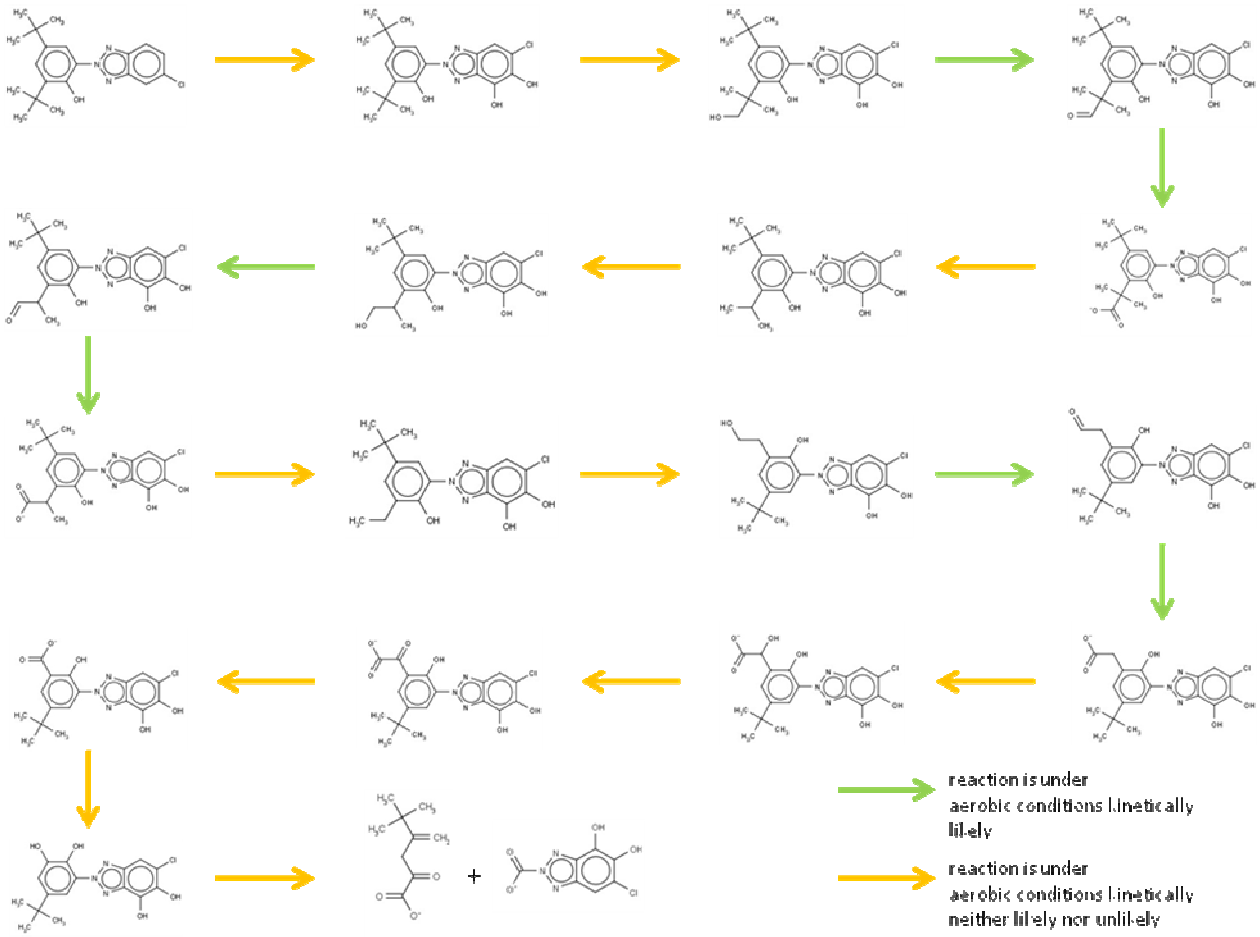
a) Degradation of the benzotriazole moiety



b) Degradation of tert-butyl side-chain in para-position to the hydroxyl group

See UV-320.

c) Degradation of the tert-butyl side-chain in ortho-position to the hydroxyl group

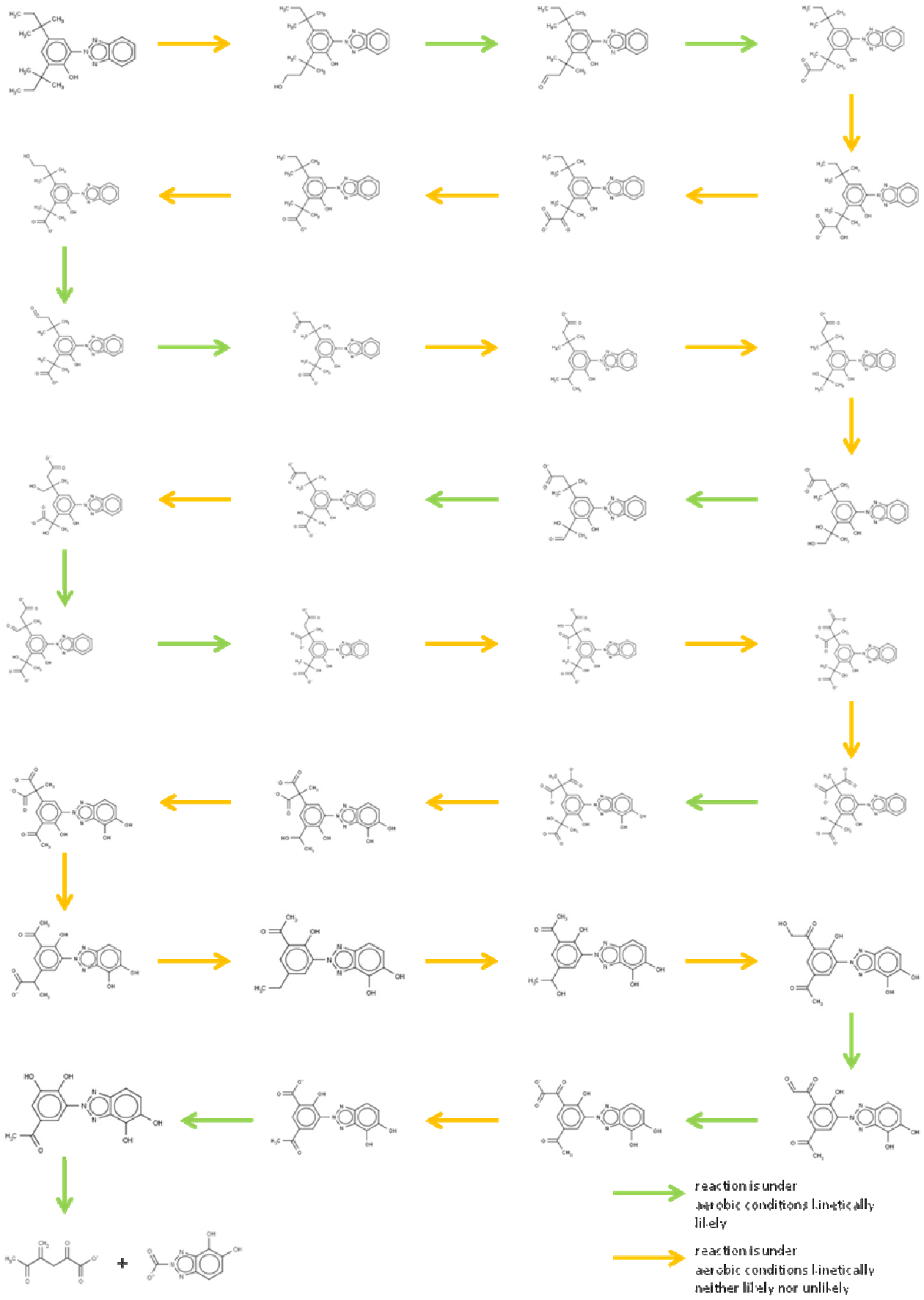


UV-328:

a) Degradation of the benzotriazole moiety

See UV-320.

b) Degradation of tert-pentyl side-chains


reaction is under aerobic conditions kinetically likely
reaction is under aerobic conditions kinetically neither likely nor unlikely

UV-350:

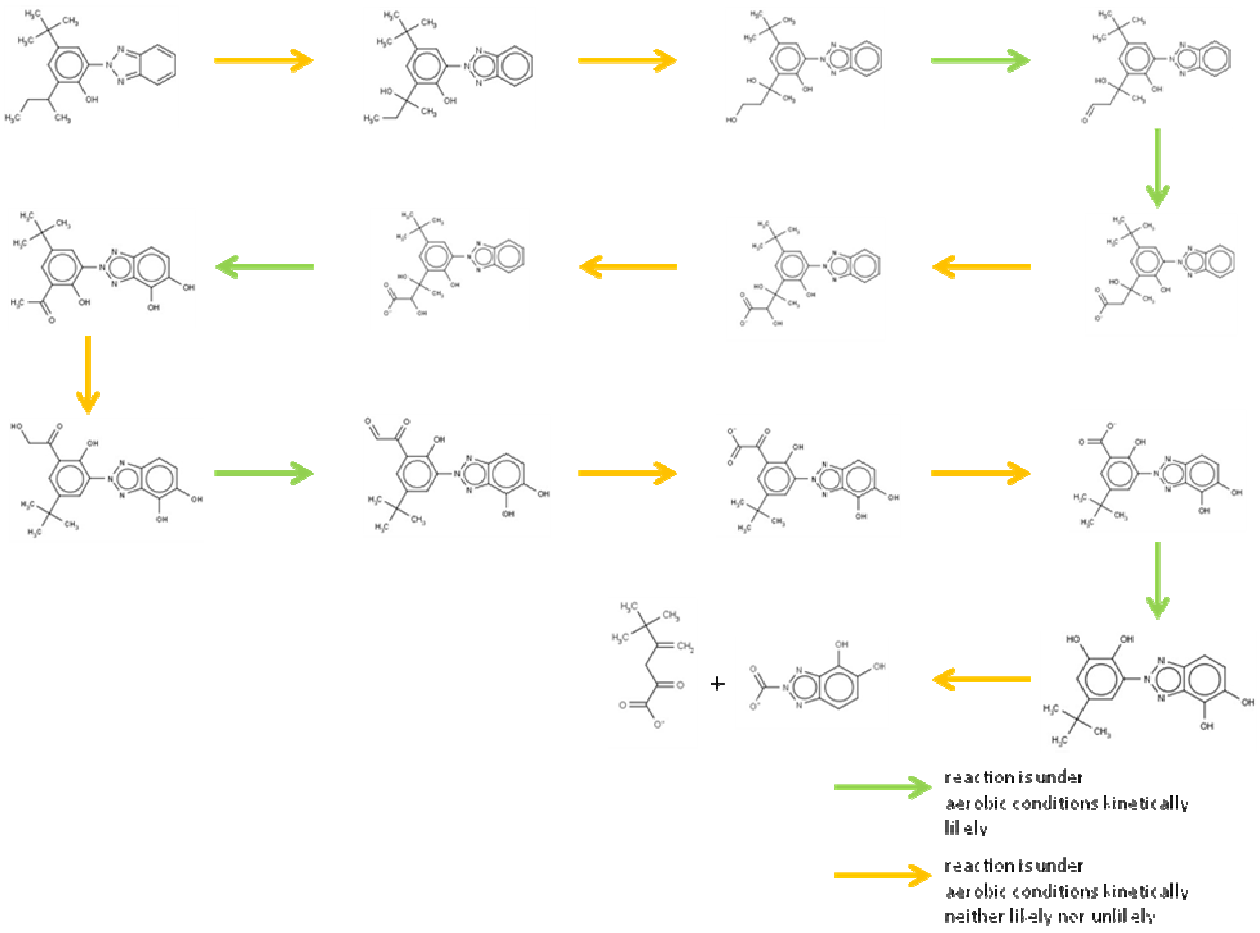
a) Degradation of the benzotriazole moiety

See UV-320.

b) Degradation of tert-butyl side-chain in para-position to the hydroxyl group

See UV-320.

c) Degradation of the sec-butyl side-chain in ortho-position to the hydroxyl group

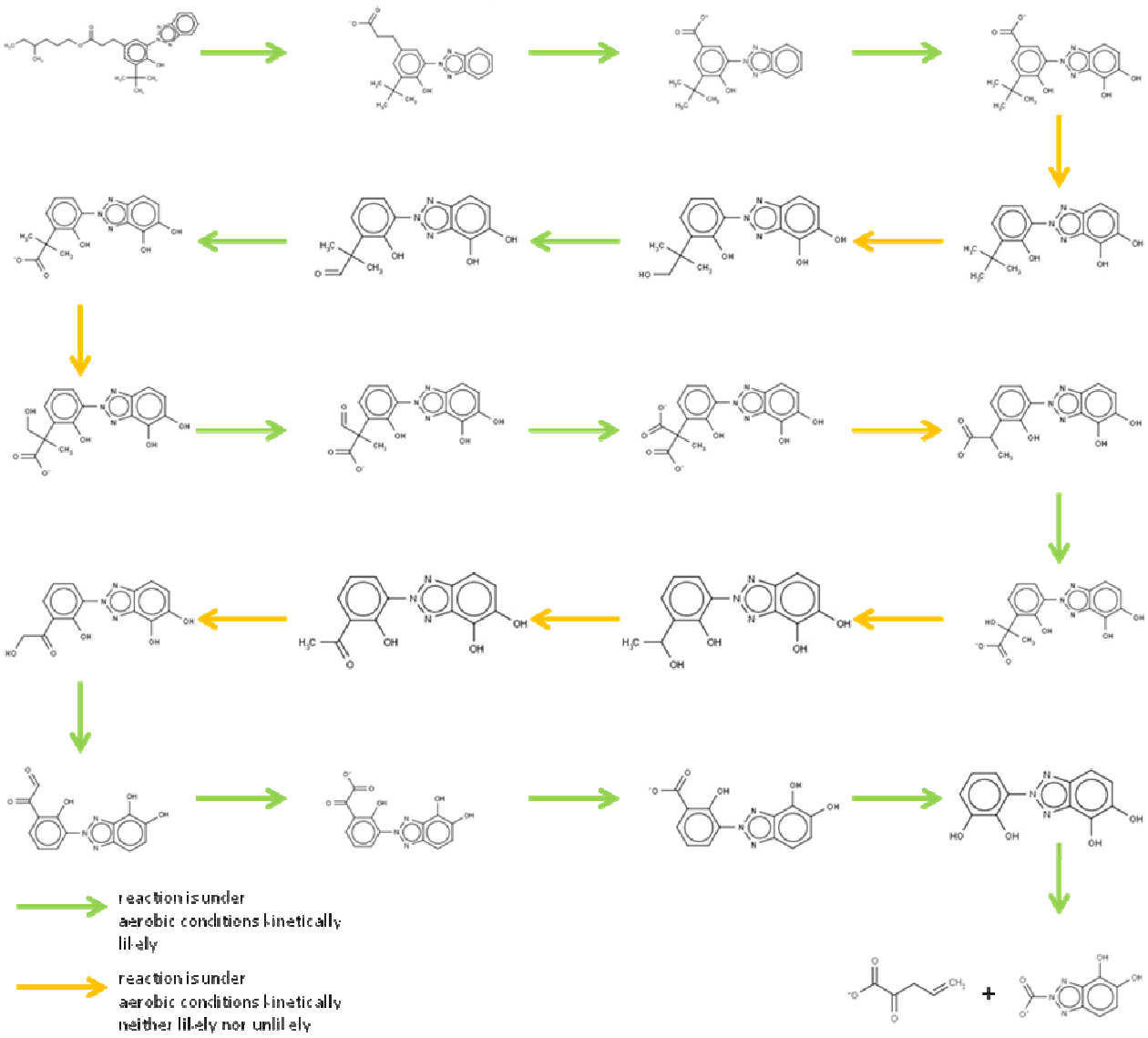


EC 407-000-3:

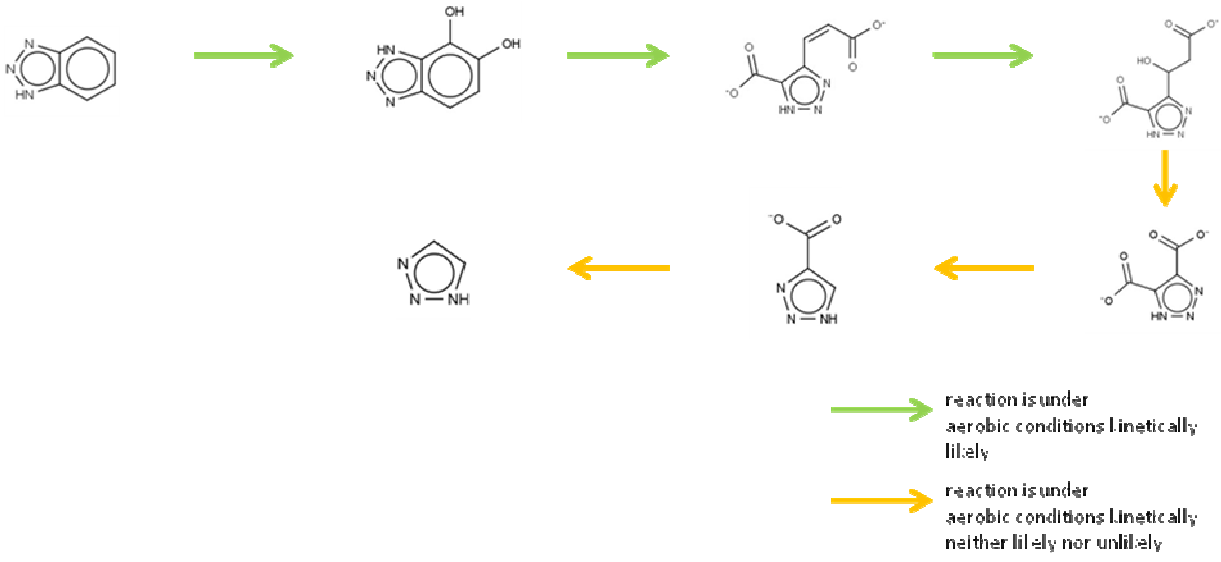
a) Degradation of the benzotriazole moiety

See UV-320.

b) Degradation of the side-chains



1H-Benzotriazole:

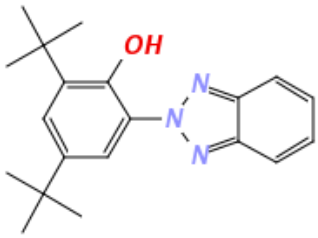


ANNEX 4: Analysis of QSAR Application: Prediction of log KOC for UV-320, -327, -328 and -350

A Information on substances and purpose

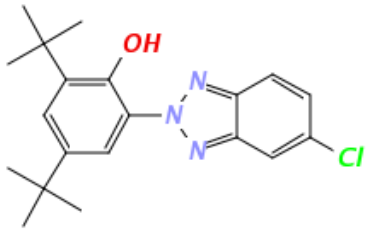
Molecule 1:

Name:	2-benzotriazol-2-yl-4,6-di-tert-butylphenol (UV-320)
CAS Nr.	3846-71-7
EU Nr.	223-346-6
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)(C)C)O)N(N=C2C=C3)N=C2C=C3



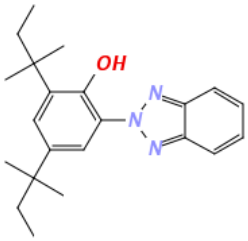
Molecule 2:

Name:	2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol (UV-327)
CAS Nr.	3864-99-1
EU Nr.	223-383-8
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)(C)C)O)N(N=C2C=C3)N=C2C=C3Cl



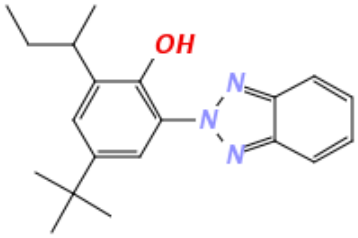
Molecule 3:

Name:	2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328)
CAS Nr.	25973-55-1
EU Nr.	247-384-8
Smiles	c1(c(c(cc(c1)C(C)(C)CC)C(C)(C)CC)O)N(N=C2C=C3)N=C2C=C3



Molecule 4:

Name:	2-(2H-benzotriazol-2-yl)-4-(tert-butyl)-6-(sec-butyl)phenol (UV-350)
CAS Nr.	36437-37-3
EU Nr.	253-037-1
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)CC)O)N(N=C2C=C3)N=C2C=C3



Endpoint	Logarithmic Partition coefficient of octanol-organic carbon
Regulatory purpose	PBT-Assessment, supporting information for a weight of evidence-approach to identify the substances as vP

B Relevant structure information

Parameter	Result	Rationale
Structure identification		
Structure of concern	parent	Substances are mono-constituents
Descriptors used for QSAR prediction		
Correction factors (KOCWIN KOW/MCI)	Applicable	All fragments are represented by the model
σ (COSMOtherm)	Applicable	The polarity was calculated on molecular structures geometrically optimized with Density-Functional-Theory (functional: Becke-Perdew 86, basis set of Triple-Zeta-Valence-Polarization-quality), all parameters for this method and all elements of the molecules are implemented
Other relevant information		
-	-	-

C QSAR models used

Model	Version	Endpoint	QMBI
(PC)KOCWIN - KOW method	V2.0	log K_{OC}	Annex4.1
(PC)KOCWIN - MCI method	V2.0	log K_{OC}	Annex 4.2
COSMOtherm (K_{OC})	v. C30_1201	log K_{OC}	Annex 4.3

D Analysis of QSAR model performance

Model	QSAR result	Overall model performance	QPREF
KOCWIN KOW method	UV-320: 4.63	Reliable with restrictions	Annex 4.4
	UV-327: 4.99		
	UV-328: 5.18		
	UV-350: 4.66		
KOCWIN MCI method	UV-320: 5.07	Reliable with restrictions	Annex 4.4
	UV-327: 5.28		
	UV-328: 5.65		
	UV-350: 5.19		
COSMOtherm (K_{OC})	UV-320: 5.17	Reliable with restrictions	Annex 4.4
	UV-327: 5.64		
	UV-328: 5.46		
	UV-350: 4.90		

E Overall conclusion

Overall QSAR Result	Irrespective of the employed model all four substances have a high log K_{OC}. There does not seem to be a general systematic shift between the models and there is also no general order of the values when comparing the relative order of the results in the three models.
Rational	The log K_{OC} for all substances and all models is in the range of 4.63 to 5.65 log-units
Reliability	Reliable with restrictions.

Conclusion with regard to the regulatory purpose
The log K_{OC}-values for all four substances are high in all three models. The predictions are all in the same region, therefore these substances are similar in their behavior. According to the prediction the substances will bind strongly to sediment in the environment and therefore will mostly not be available for degradation processes.

ANNEX4.1: QMBI KOCWIN KOW-method

	Information	Literature references or Links	Remarks
0 - General			
Model name and version	(PC)KOCWIN v.2 - KOW method	Online Help of KOCWIN	The KOCWIN – KOW method is essentially an extension of the MCI method were the descriptor MCI was replaced with K_{OW}. The same Trainings Sets and Validation Sets as for the MCI method were used and also the same Correction factors are applied. Overall the statistical performance of the KOW method is not quite as good as the MCI method.
W.a.[17]: software package	EPISUITE Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10	http://www.epa.gov/oppt/exposure/pubs/episuite.htm	
1 - Definition of Endpoint			
Endpoint [units] (w.a. species and other relevant information)	Soil adsorption coefficient K_{OC} given as a logarithmic value		Definition of K_{OC} according to Lyman et al, 1990: "the ratio of the amount of chemical adsorbed per unit weight of organic carbon (oc) in the soil or sediment to the concentration of the chemical in solution at equilibrium" Koc = (µg adsorbed/g organic carbon) / (µg/mL solution) [L/kg or mL/g]
2 – Definition of Algorithm			
Brief description of algorithm and/or link to full definition	Non-polar chemicals (i.e. compounds where no correction factor is needed): log K_{oc} = 0.8679 Log K_{ow} - 0.0004 Polar chemicals (i.e. compounds where a correction factor is needed): log K_{oc} = 0.55313 Log K_{ow} + 0.9251 + $\Sigma P_f N$	See Online Help of KOCWIN	The equations were developed in a two separate regression calculations since this approach is statistically more accurate than the approach taken in the MCI-method
List of employed	Log KOW: logarithm of the n-octanol/water partition coefficient; P_f: correction factor for	List of P_f available in Online Help of KOCWIN, Appendix D	

[17] w.a.: when applicable

descriptors with units	chemical class of functional group f; N: number of times chemical class or functional group f occurs		
Number of Chemicals in Training Set and Brief description of it	Training Set comprises of non-polar set (68 chemicals) and a polar set (447 chemicals) taken from several literature sources. One compound of the original non-polar training set (hexabromobiphenyl) was not considered since there was no recommended experimental log K_{OW}.		Training Estimation Error: within <= 0.20 - 44.2% within <= 0.40 - 76.9% within <= 0.60 - 93.0% within <= 0.80 - 98.6% within <= 1.00 - 100% non-polar Training Set (n=68): r^2=0.877; std. dev.=0.478; avg. dev.= 0.371 polar Training Set (n=447): r^2=0.855; std. dev.=0.396; avg. dev.= 0.307
W.a.: Training set available at		Non-Polar Training Set: Online Help of KOCWIN, Appendix E Polar Set: Online Help of KOCWIN, Appendix F	
3 – Definition of the Applicability Domain			
W.a.: Definition of the Applicability Domain	Currently there is no universally accepted definition of model domain. Log Koc estimates are less accurate for compounds outside the MW range of the training set compounds and/or that have more instances of a given fragment than the maximum for all training set compounds. It is also possible that a compound may have a functional group(s) or other structural features not represented in the training set, and for which no fragment coefficient or correction factor was developed	List of correction factors available in Online Help of KOCWIN, Appendix D Non-Polar Training Set: Online Help of KOCWIN, Appendix E Polar Training Set: Online Help of KOCWIN, Appendix F	
Limits of the Applicability Domain	Molecular weight: 32.04-665.02 g/Mol Fragments and Functional groups according to Training Sets and correction factors for best results		
4 – Information on the Validation of the Model			
Validation Set Type	Internal, 150 compounds from the same sources as the Training Set. Eight ammonium and metal salt compounds were		

	removed from the original Validation dataset of the MCI method. Compound Pool was split before regression into Training Set and Validation Set.		
W.a.: Validation available at		Online Help of KOCWIN, Appendix G	
Statistical information on validity	r^2=0.778; std. dev.=0.679; avg. dev.= 0.494		
5 – Mechanistic Interpretation of the model			
W.a.: Mechanistic basis of model	The tendency of a compound to adsorb itself on organic carbon is linked with its lipophilicity. The n-octanol/water partition coefficient is one descriptor for lipophilicity.		

ANNEX 4.2: QMBI KOCWIN MCI-method

	Information	Literature references or Links	Remarks
0 – General			
Model name and version	(PC)KOCWIN v.2 - MCI method	Meylan, W., P.H. Howard and R.S. Boethling, "Molecular Topology/Fragment Contribution Method for Predicting Soil Sorption Coefficients", *Environ. Sci. Technol*. 26: 1560-7 (1992)	Besides the MCI method there is also the KOW method implemented in KOCWIN. Overall the statistical performance of the MCI method is better than the KOW method.
W.a.[18]: software package	EPISUITE Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10	http://www.epa.gov/oppt/exposure/pubs/episuite.htm	
1 - Definition of Endpoint			
Endpoint [units] (w.a. species and other relevant information)	Soil adsorption coefficient K_{OC} given as a logarithmic value		Definition of K_{OC} according to Lyman et al, 1990: "the ratio of the amount of chemical adsorbed per unit weight of organic carbon (oc) in the soil or sediment to the concentration of the chemical in solution at equilibrium" Koc = (µg adsorbed/g organic carbon) / (µg/mL solution) [L/kg or mL/g]
2 – Definition of Algorithm			
Brief description of algorithm and/or link to full definition	log Koc = 0.5213 MCI + 0.60 + $\Sigma(P_f*N)$; MCI = $\Sigma(\delta i*\delta j)^{-0.5}$	See Online Help of KOCWIN	MCI: Molecular Connectivity Index (in this case: First Order) mathematical approach to describe molecular topology The equation was developed in a two step regression approach: 1. Derivation of equation without correction factors using a set of non polar chemicals

[18]w.a.: when applicable

			2. Derivation of final equation using a set of non-polar chemicals
List of employed descriptors with units	δi: δ-value of atom i, i.e. the number of adjacent non-hydrogen atoms; δj: δ–value of atom j, i.e. the number of adjacent non-hydrogen atoms; P_f: correction factor for chemical class of functional group f; N: number of times chemical class or functional group f occurs	List of P_f available in Online Help of KOCWIN, Appendix D	
Number of Chemicals in Training Set and Brief description of it	Training Set comprises of non-polar set (69 chemicals) and a polar set (447 chemicals) taken from several literature sources		Training Set Estimation Error: within <= 0.20 - 44.2% within <= 0.40 - 76.9% within <= 0.60 - 93.0% within <= 0.80 - 98.6% within <= 1.00 - 100% non-polar Training Set (n=69): r^2=0.967; std. dev.=0.247; avg. dev.= 0.199 polar Training Set (n=447): r^2=0.90; std. dev.=0.34; avg. dev.= 0.273
W.a.: Training set available at		Non-Polar Training Set: Online Help of KOCWIN, Appendix E Polar Set: Online Help of KOCWIN, Appendix F	
3 – Definition of the Applicability Domain			
W.a.: Definition of the Applicability Domain	Currently there is no universally accepted definition of model domain. Log Koc estimates are less accurate for compounds outside the MW range of the training set compounds and/or that have more instances of a given fragment than the maximum for all training set compounds. It is also possible that a compound may have a functional group(s) or other structural features not represented in the training set, and for which no fragment	List of correction factors available in Online Help of KOCWIN, Appendix D Non-Polar Training Set: Online Help of KOCWIN, Appendix E Polar Training Set: Online Help of KOCWIN, Appendix F	

	coefficient or correction factor was developed		
Limits of the Applicability Domain	Molecular weight: 32.04-665.02 g/Mol Fragments and Functional groups according to Training Sets and correction factors for best results		
4 – Information on the Validation of the Model			
Validation Set Type	Internal, 158 compounds from the same sources as the Training Set. Compound Pool was split before regression into Training Set and Validation Set.		
W.a.: Validation available at		Online Help of KOCWIN, Appendix G	
Statistical information on validity	r^2=0.850; std. dev.=0.583; avg. dev.= 0.459		
5 – Mechanistic Interpretation of the model			
W.a.: Mechanistic basis of model	The tendency of a compound to adsorb itself on organic carbon is linked with the chemical structure. In the Molecular Correction Index information on the chemical structure, i.e. molecular size, branching, cyclization, unsaturation and (to a certain extent) heteroatom content are encoded. The different influences of chemical classes or functional groups are considered by correction factors.		

ANNEX4.3: QMBI COSMOtherm (K_{OC})

	Information	Literature references or Links	Remarks
0 - General			
Model name and version	COSMOtherm v C30_1201		The COSMOtherm model allows in principle the calculation of all partition properties of molecules. In this QMBI only the calculation of the K_{OC} will be addressed
W.a.[19]: software package	COSMOtherm		
1 - Definition of Endpoint			
Endpoint [units] (w.a. species and other relevant information)	n-octanol/organic carbon partition coefficient given as a logarithmic value		
2 – Definition of Algorithm			
Brief description of algorithm and/or link to full definition	Log K_{OC} = 0.0168*M_0^X – 0.017*M_2^X – 0.040*M_3^X + 0.19*PM_{acc}^X – 0.27*M_{don}^X + 0.37 with $M_i^X = \int p^X \sigma^i d\sigma$ for i = 0, 2, 3. M_{acc}^X = 0 if $\sigma < 1$ e/nm^2 or = σ – 1 e/nm^2 if $\sigma > 1$ e/nm^2 and M_{don}^X = 0 if $-\sigma < 1$ e/nm^2 or = -σ – 1 e/nm^2 if $-\sigma > 1$ e/nm^2	"COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design", Andreas Klamt, Elsevier Science Ltd., Amsterdam, The Netherlands (2005), ISBN: 0-444-51994-7. "Prediction Of Soil Sorption Coefficients With A Conductor-Like Screening Model For Real Solvents", Andreas Klamt, Frank Eckert and Michael Diedenhofen, *Environmental Toxicology and Chemistry*, **21**, 2562-2566 (2002).	COSMOtherm implements the COSMO-RS theory. This theory interprets the interaction of molecules as an interaction of a larger ensemble of molecular surfaces calculated with Quantum Mechanical methods. Due to a treatment with statistical thermodynamics the macroscopic properties of interacting molecules like partition coefficients become available. If the partition is with a phase that is ill defined like organic carbon, the so called σ-moment approach is employed where a solvent is represented as a linear combination of six σ-functions. The coefficients to these functions are fitted with experimental data.
List of employed descriptors with units	σ: Screening charge density or polarity, i.e. the electrostatic screening of a solute molecule by its surrounding and its back polarization in a region with radius of ca. 0.5 Å ; p^X: sigma profile of molecule X, i.e. the sum of the probability distributions of all possible σ		

[19] w.a.: when applicable

Number of Chemicals in Training Set and brief description of it	Original parameterization for COSMOtherm: 225 small- and medium-sized organic compounds with H, C, O, N, Cl atoms. The fitting was done for 650 experimental room-temperature parameters (ΔG_{hydr}, log(vapor pressure), log $K_{octanol-water}$, log $K_{hexane-water}$, log $K_{benzene-water}$, log $K_{diethyl\ ether-water}$ log K_{OC}-formula: 387 molecules (performance: r^2 = 0.72, rms = 0.62 log-units)		While the principle theory is applicable for all elements, the practical implementation needs some specific parameters to the QM-method used and the elements of the substance in question like the employed ratio for scaling the bonds of the QM-method and the van der Waals-coefficients
W.a.: Training set available at		Original parameterization for COSMOtherm: "Refinement and Parametrization of COSMO-RS", Andreas Klamt, Volker Jonas, Thorsten Bürger and John C. W. Lohrenz, *J. Phys. Chem. A* **102**, 5074-5085 (1998). Log K_{OC}-formula: "Prediction Of Soil Sorption Coefficients With A Conductor-Like Screening Model For Real Solvents", Andreas Klamt, Frank Eckert and Michael Diedenhofen, *Environmental Toxicology and Chemistry*, **21**, 2562-2566 (2002).	Original parameterization for COSMOtherm: Since the original parameterization was done further adjustments were made and parameters for further elements were introduced. While the parameters are available in the software, to our knowledge the details of the new parameterisations were not disclosed
3 – Definition of the Applicability Domain			
W.a.: Definition of the Applicability Domain	There is no formal definition of the applicability domain		
Limits of the Applicability Domain	In principle the method is completely based on first-principles meaning there is no limit of the Applicability Domain.		
4 – Information on the Validation of the Model			
Validation Set Type	The KOC-model was tested against 53 demanding chemicals achieving a rmd of 0.72		
W.a.: Validation available at		"Prediction Of Soil Sorption Coefficients With A Conductor-Like Screening Model For Real Solvents", Andreas Klamt, Frank Eckert and	

		Michael Diedenhofen, *Environmental Toxicology and Chemistry*, **21**, 2562-2566 (2002).	
Statistical information on validity	-		
5 – Mechanistic Interpretation of the model			
W.a.: Mechanistic basis of model	The interaction of a solute and a solvent is calculated in terms of a chemical potential. The difference of the chemical potentials of the solute in two different solvents is the mechanistic reason for partition effects.		

ANNEX 4.4: Analysis of QSAR prediction for UV-320 , UV-327, UV-328, UV-350

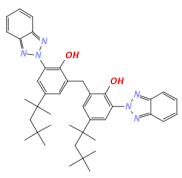
QSAR Model: KOCWIN KOW-method, KOCWIN MCI-method and COSMOtherm (K_{OC})

Overall performance

	Result		**Further description**
Endpoint results [unit]	KOCWIN KOW-method	UV-320: 4.63	All log KOC-values are high and in a similar region.
		UV-327: 4.99	
		UV-328: 5.18	
		UV-350: 4.66	
	KOCWIN MCI-method	UV-320: 5.07	
		UV-327: 5.28	
		UV-328: 5.65	
		UV-350: 5.19	
	COSMOtherm (K_{OC})	UV-320: 5.17	
		UV-327: 5.64	
		UV-328: 5.46	
		UV-350: 4.90	
Applicability domain	Yes		The molecules are in the range of all descriptors employed in the models.
Similarity with trainings set	Yes		All fragments or elements of the molecules are represented in the Training Set of KOCWIN. COSMOtherm has no training set but is generally applicable.
Similar substances	One		See table next side, substance is not very similar
Model performance for similar substances	Mediocre		There is just one experimental value of unknown quality for a substance not very similar to the substances at hand. The prediction for this substance is much higher than the experimental value but both values are high.
Other uncertainties	No		-

Overall conclusion	Reliable
Rational	As the models are applicable and results for similar molecules and two of the four models at hand show values in the same range it can be expected that the range is correctly predicted.

Results for similar substances

	Substance 1
Structure	
CAS-Nr.	103597-45-1
EU-Nr.	403-800-1
(Trade-)Name	UV-360
Descriptor value	KOCWIN KOW-method : log K_{OC} = 11.08 KOCWIN KOW-method : log K_{OC} = 8.22 COSMOtherm:

	log K_{OW} = 7.91
Predicted endpoint	See above
Experimental endpoint	5.63
Statistical performance	-

Rationale for the selection of similar substances

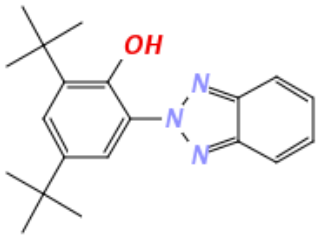
Substance 1 is a phenolic benzotriazole as the target molecule but it is a molecule comprised of two phenolic benzotriazole bodies therefore the similarity is not very high. Since the functional groups are nevertheless the same and since there are no other phenolic benzotriazoles were a experimental log K_{OC} is reported, UV-360 was chosen as point of reference.

ANNEX 5: Analysis of QSAR Application: Prediction of log KOW for UV-320, -327, -328 and -350

A Information on substances and purpose

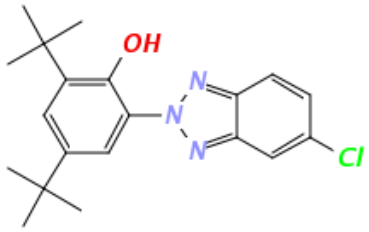
Molecule 1:

Name:	2-benzotriazol-2-yl-4,6-di-tert-butylphenol (UV-320)
CAS Nr.	3846-71-7
EU Nr.	223-346-6
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)(C)C)O)N(N=C2C=C3)N=C2C=C3



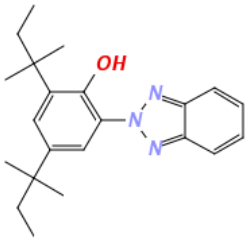
Molecule 2:

Name:	2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol (UV-327)
CAS Nr.	3864-99-1
EU Nr.	223-383-8
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)(C)C)O)N(N=C2C=C3)N=C2C=C3Cl



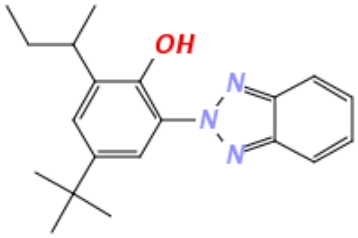
Molecule 3:

Name:	2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328)
CAS Nr.	25973-55-1
EU Nr.	247-384-8
Smiles	c1(c(c(cc(c1)C(C)(C)CC)C(C)(C)CC)O)N(N=C2C=C3)N=C2C=C3



Molecule 4:

Name:	2-(2H-benzotriazol-2-yl)-4-(tert-butyl)-6-(sec-butyl)phenol (UV-350)
CAS Nr.	36437-37-3
EU Nr.	253-037-1
Smiles	c1(c(c(cc(c1)C(C)(C)C)C(C)CC)O)N(N=C2C=C3)N=C2C=C3



Endpoint	Logarithmic Partition coefficient of octanol-water
Regulatory purpose	PBT-Assessment, supporting information

B Relevant structure information

Parameter	Result	Rationale
Structure identification		
Structure of concern	parent	Substances are mono-constituents
Descriptors used for QSAR prediction		
Fragment descriptors (KOWWIN)	applicable	All fragments are represented by the model
σ (COSMOtherm)	applicable	The polarity was calculated on molecular structures geometrically optimized with employing Density-Functional-Theory (functional: Becke-Perdew 86, basis set of Triple-Zeta-Valence-Polarization-quality), all parameters for this method and all elements of the molecules are implemented
Other relevant information		
-	-	-

C QSAR models used

Model	Version	Endpoint	QMBI
KOWWIN	v1.68	log K_{OW}	Annex 5.1
COSMOtherm (K_{OW})	v. C30_1201	log K_{OW}	Annex 5.2

D Analysis of QSAR model performance

Model	QSAR result	Overall model performance	QPREF
KOWWIN	UV-320: 6.27	Reliable	Annex 5.3
	UV-327: 6.91		
	UV-328: 7.25		
	UV-350: 6.31		
COSMOtherm (K_{OW})	UV-320: 7.39	Reliable	Annex 5.3
	UV-327: 7.91		
	UV-328: 7.89		
	UV-350: 7.11		

E Overall conclusion

Overall QSAR Result	All four substances have a very high log K_{OW} that is above the screening criterion for bioaccumulation in the PBT-assessment. The substances behave similar. Also KOWWIN predicts log KOWs approximately 0.8-1.0 log units smaller than COSMOtherm. The values of KOWWIN are nearer to the available experimental values.
Rationale	Not B-Screening criteria according to ECHA Guidance R.11 is log K_{OW} < 4.5
Reliability	Reliable

Conclusion with regard to the regulatory purpose
The log K_{OW}-values for all four substances are high and therefore a high bioaccumulation potential is expected. This expectation is confirmed by the available experimental BCF-values. All four substances have log K_{OW}-values in the same region. While there seems to be a systematic shift between the results there is no such shift observed for the relative order of the values.

ANNEX 5.1: QMBI KOWWIN

	Information	Literature references or Links	Remarks
0 - General			
Model name and version	KOWWIN 1.68	Meylan, W.M. and P.H. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84: 83-92.	
W.a.[20]: software package	EPISUITE Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10	http://www.epa.gov/oppt/exposure/pubs/episuite.htm	
1 - Definition of Endpoint			
Endpoint [units] (w.a. species and other relevant information)	n-octanol/water partition coefficient given as a logarithmic value		
2 – Definition of Algorithm			
Brief description of algorithm and/or link to full definition	Log K_{OW} = $\Sigma(f_i*n_i)+ \Sigma (c_j*n_j)$ + 0.229	See Online help of KOWWIN	Derived by multiple regression of training set in a two step procedure: 1. Derivation of f_i 2. Introduction of c_j
List of employed descriptors with units	f_i: coefficient for each atom or fragment i; n_i: number of times fragment/atom i occurs; c_j: coefficient for correction instance j; number of times a structure that leads to a correction instance occurs	See Online help of KOWWIN, Appendix D	There are 157 different atoms and fragments defined and 278 correction factors that are employed when certain chemical classes or functional groups are present in the molecule for which an estimation is made
Number of Chemicals in Training Set and Brief description of it	2447 chemicals with measured log K_{OW}-values from the PhysProp Database		Training Set Estimation Error: within <= 0.10 - 45.0% within <= 0.20 - 72.5% within <= 0.40 - 92.4% within <= 0.50 - 96.4% within <= 0.60 - 98.2%
W.a.: Training set available at		List available at http://esc.syrres.com/interkow/KowwinData.htm	
3 – Definition of the Applicability Domain			

[20]w.a.: when applicable

W.a.: Definition of the Applicability Domain	Currently there is no universally accepted Applicability Domain, but in principle by molecular weight range and by fragments and their maximum occurrence, both defined by the Training Set; while also substances with specific behavior in liquids like dissociation or surfactant-specific properties were included, these are not explicitly considered in the model		With exceedingly high or low log K_{OW} the experimental errors for determination of log K_{OW} will become larger and therefore the uncertainty. In such cases the predicted values will be more uncertain as well.
Limits of the Applicability Domain	18.02 to 719.92 [g/Mol], for Structural Domain see Training Set		
4 – Information on the Validation of the Model			
Validation Set Type	Approximately 10.946 chemicals from different sources		
W.a.: Validation available at		List available at http://esc.syrres.com/interkow/KowwinData.htm	
Statistical information on validity	Validation Set Estimation Error: within <= 0.20 - 39.6% within <= 0.40 - 66.0% within <= 0.50 - 75.6% within <= 0.60 - 82.5% within <= 0.80 - 91.6% within <= 1.00 - 95.6% within <= 1.20 - 97.7% within <= 1.50 - 99.1%		Details available in Online help of KOWWIN
5 – Mechanistic Interpretation of the model			
W.a.: Mechanistic basis of model	Fragment coefficients and correction factors reflect the impact of certain chemical fragments or functional groups on lipophilicity and thus on the log K_{OW}.		

ANNEX 5.2: QMBI COSMOtherm KOW

	Information	Literature references or Links	Remarks
0 - General			
Model name and version	COSMOtherm v C30_1201		The COSMOtherm model allows in principle the calculation of all partition properties of molecules. In this QMBI only the calculation of the K_{OW} will be addressed
W.a.[21]: software package	COSMOtherm		
1 - Definition of Endpoint			
Endpoint [units] (w.a. species and other relevant information)	n-octanol/water partition coefficient given as a logarithmic value		
2 – Definition of Algorithm			
Brief description of algorithm and/or link to full definition	log K_{OW} (T)= $\int p^i(\sigma)(\propto_{water}(\sigma;T) - \propto_{octanol}(\sigma;T))d\sigma + \propto_i^C(water, T) - \propto_i^C(octanol,; T)$, where $\propto_i^C(S, T) = RT^* [\lambda_0^* \ln r_i + \lambda_1^*(1-(r_i/\underline{r} - \ln \underline{r}) + \lambda_2^*(1-q_i/\underline{q} - \ln \underline{q})]$ and $\underline{r} = \Sigma_I x_i^* r_i$ and $\underline{q} = \Sigma_i x_i^* q_i$	"COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design", Andreas Klamt, Elsevier Science Ltd., Amsterdam, The Netherlands (2005), ISBN: 0-444-51994-7.	COSMOtherm implements the COSMO-RS theory. This theory interprets the interaction of molecules as an interaction of a larger ensemble of molecular surfaces calculated with Quantum Mechanical methods. Due to a treatment with statistical thermodynamics the macroscopic properties of interacting molecules like partition coefficients become available.
List of employed descriptors with units	R: Ideal gas constant [kcal/(mol K)], T: temperature [K]; σ: Screening charge density or polarity, i.e. the electrostatic screening of a solute molecule by its surrounding and its back polarization in a region with radius		

[21] w.a.: when applicable

	of ca. 0.5 Å ; $p^i(\sigma)$: sigma profile of molecule i, i.e. the sum of the probability distributions of all possible σ; $\propto_{water}(\sigma;T)$: sigma potential of water at temperature T, a sigma potential can be interpreted as the affinity of a molecule for a surface of polarity σ; $\propto_{octanol}(\sigma;T)$: sigma potential of octanol at temperature T; $\propto_i^C(S;T)$: combinatorial contribution to the chemical potential of molecule i in solvent S at temperature T; λ_0, λ_1, λ_2: adjustable parameters, r_i: molecular volume of substance i, q_i: molecular area of substance i, r: overall volume of the mixture, q: overall area of the mixture.		
Number of Chemicals in Training Set and brief description of it	Original parameterisation: 225 small- and medium-sized organic compounds with H, C, O, N, Cl atoms. The fitting was done for 650 experimental room-temperature parameters (ΔG_{hydr}, log(vapor pressure), log $K_{octanol-water}$, log $K_{hexane-water}$, log $K_{benzene-water}$, log $K_{diethyl\ ether-water}$		While the principle theory is applicable for all elements, the practical implementation needs some specific parameters to the QM-method used and the elements of the substance in question like the employed ratio for scaling the bonds of the QM-method and the van der Waals-coefficients
W.a.: Training set available at		"Refinement and Parametrization of COSMO-RS", Andreas Klamt, Volker Jonas, Thorsten Bürger and John C. W. Lohrenz, *J. Phys. Chem. A* **102**, 5074-5085 (1998).	Since the original parameterization was done further adjustments were made and parameters for further elements were introduced. While the parameters are available in the software, to our knowledge the details of the new parameterisations were not disclosed
3 – Definition of the Applicability Domain			
W.a.: Definition of	There is no formal definition of the applicability domain		

the Applicability Domain			
Limits of the Applicability Domain	In principle the method is completely based on first-principles meaning there is no limit of the Applicability Domain.		
4 – Information on the Validation of the Model			
Validation Set Type	To our knowledge there is no single validation set but there are several citations in literature on the accuracy/validity of the model		
W.a.: Validation available at		Overview over publications: http://www.cosmologic.de/index.php?cosId=4150&crId=10	
Statistical information on validity	-		
5 – Mechanistic Interpretation of the model			
W.a.: Mechanistic basis of model	The interaction of a solute and a solvent is calculated in terms of a chemical potential. The difference of the chemical potentials of the solute in two different solvents is the mechanistic reason for partition effects.		

ANNEX 5.3: Analysis of QSAR prediction for UV-320 , UV-327, UV-328, UV-350

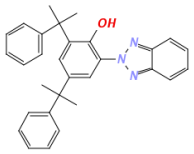
QSAR Model: KOWWIN and COSMOtherm (K_{OW})

Overall performance

	Result		**Further description**
Endpoint results [unit]	KOWWIN	UV-320: 6.27	All log KOW-values are high and in a similar region. There seems to be a systematic shift between the two models where KOWWIN predicts in general lower values.
		UV-327: 6.91	
		UV-328: 7.25	
		UV-350: 6.31	
	COSMO-therm (K_{OW})	UV-320: 7.39	
		UV-327: 7.91	
		UV-328: 7.89	
		UV-350: 7.11	
Applicability domain	Yes		The molecules are in the range of all descriptors employed in the models and in the range of the molecular weight of the molecules in the training set of KOWWIN.
Similarity with trainings set	Yes		All fragments or elements of the molecules are represented in the Training Set of KOWWIN. COSMOtherm has no training set but is generally applicable.
Similar substances	Yes		See table next side
Model performance for similar substances	Concerning the range of values good, but absolute values seem to be slightly overestimated		Experimental Values and predictions show a systematic shift but caution has to be advised as the experimental values were not validated.
Other uncertainties	No		-

Overall conclusion	Reliable
Rational	As the models are applicable and results for similar molecules and two of the four models at hand show values in the same range it can be expected that the range is correctly predicted.

Results for similar substances

	Substance 1
Structure	
CAS-Nr.	70321-86-7
EU-Nr.	274-570-6
(Trade-)Name	UV-234
Descriptor value	KOWWIN : log K_{OW} = 7.67 COSMOtherm: log K_{OW} = 8.30
Predicted endpoint	See above
Experimental endpoint	> 6.5
Statistical performance	-

Rationale for the selection of similar substances

Substance 1 is structurally similar as it is a phenolic benzotriazole as the target molecule. It also has a sterical demanding side chain in ortho- and one in para-position to the hydroxyl group. The difference lies in the substitution of a phenyl group for a methyl group. Therefore is is probably to some degree more lipophilic as UV-327.

ANNEX 6: Monitoring Study Results for UV-320, UV-327, UV-328, UV- 350

Monitoring of phenolic benzotriazoles

Monitoring studies are summarized concerning the following phenolic benzotriazoles: UV-234 (CAS 70-321-86-7), -320 (CAS 3846-71-7), -326 (CAS 3896-11-5), -327 (CAS 3864-99-1), -328 (CAS 25973-55-1), -329 (CAS 3147-75-9), -350 (CAS 36437-37-3), -360 (CAS 103597-45-1) and -571 (CAS 125304-04-3). No monitoring studies were found for UV-928 (CAS 73936-91-1).

European studies:

Brorström-Lundén et al. (Brorström-Lundén et al., 2011) published a screening study on benzotriazoles (UV-234, -320, -327, -328, -329, -360). Phenolic benzotriazoles may to a large extent enter Sweden through imported finished goods. Emissions via diffuse sources were assumed as the main pathway of benzotriazole UV-absorbers to the environment. The sampling program was therefore focused on emissions in urban environments (Stockholm area and smaller city Borås). In addition background sites were included and two sites with potential point sources. Benzotriazoles were analyzed using an LC-MS system including a tandem mass-spectrometer. Detection limits vary with analyzed substance and sample. Compared to other studies the detection limits for sediment, soil, particles, WWTP sludge and fish are high.

Table 25: Detection limits in the investigation of Brorström-Lundén et al.

Compartment	Detection limits	Compartment	Detection limits
Air	0.01 – 0.48 ng/m³	storm water	0.03 – 0.1 ng/L
air deposition	30 – 200 ng/m² day	landfill effluent particles	0.7 -1.6 µg/g dw
surface water	0.03 – 0.09 ng/L	landfill effluent	0.08 – 0.5 ng/L
Sediment	0.2 – 12 µg/g dw	WWTP effluent particles	61 – 130 µg/g dw
Soil	0.1 – 0.9 µg/g dw	WWTP effluent	0.04 – 0.1 ng/L
Fish	0.3 – 1.9 µg/g dw	sludge	0.1 – 0.6 µg/g dw

In air samples 4 benzotriazole UV-absorbers were detected (UV-320, -327, -329, -360). Concentrations were similar in background and urban air. However, the highest concentration was measured in Stockholm. Only two compounds were detected in atmospheric deposition (UV-327, -329). The deposition was higher at the urban site.

Table 26: Concentrations of phenolic benzotriazoles in air and atmospheric deposition in Sweden

Substance	Air		Deposition	
	detected in x of y samples [x/y]	concentration [ng/m³]	detected in x of y samples [x/y]	deposition flux [ng/m² day]
UV-234	0/8	-	0/4	-
UV-320	3/8	0.024 – 0.67	0/4	-
UV-327	6/8	0.40 - 25	3/4	<100-320
UV-328	0/8	-	0/4	-
UV-329	5/8	< 0.15 – 3.0	3/4	<100-331
UV-360	1/8	0.40	0/4	-

Several benzotriazoles were found in soil, in rather similar concentrations at the background and the urban locations (UV-320, -327, -328, -329). There were differences in the occurrence among the individual substances at the different locations. According to the authors the highest concentration of a single substance (UV-329) was found in Soil 500 m from a busy road in the Stockholm area. However, according to the annex of the

study such a high concentration was also found for UV-327 in another urban sample. Since only 4 samples were analyzed altogether, the results should generally be interpreted with care.
Several of the benzotriazoles were frequently detected in surface water (UV-320, -327, -328. -329). The concentrations were mostly similar at background and urban locations. In sediments the distribution among different substances varied for the different sampling sites. Peaks of single substances occurred both at background and urban locations; the lower concentration levels were similar at different locations.
Three of the benzotriazoles were found in fish, both at urban and background locations (UV-324, -327, -329). The highest concentration was found at the background location (UV-327). The concentrations found in Swedish fish are 1000fold higher than those found in Japanese fish. The reason for this is unknown. The authors note however that most substances are not detected and the levels found are quite close to the detection limit of the method used.

Table 27: Concentrations of phenolic benzotriazoles in soil and fish in Sweden

Substance	**Soil**		**Fish**	
	detected in x of y samples [x/y]	concentration [µg/g dw]	detected in x of y samples [x/y]	concentration [µg/g dw]
UV-234	0/4	-	1/4	0.26
UV-320	1/4	0.91	0/4	-
UV-327	3/4	0.66-3.7	3/4	2.3-9.8
UV-328	1/4	0.74	0/4	-
UV-329	3/4	0.79-3.7	3/4	1-2.5
UV-360	0/4	-	0/4	-

Table 28: Concentrations of phenolic benzotriazoles in surface water and sediment in Sweden

Substance	**Surface water**		**sediment**	
	detected in x of y samples [x/y]	concentration [ng/L]	detected in x of y samples [x/y]	concentration [µg/g dw]
UV-234	0/6	-	0/6	-
UV-320	3/6	0.55-0.94	5/6	0.16-3
UV-327	4/6	0.11-0.39	6/6	1.6-35
UV-328	6/6	1.3-10	4/6	0.65-1.3
UV-329	6/6	0.25-2.4	4/6	0.81-33
UV-360	1/6	0.16	3/6	0.42-2.9

All benzotriazoles but UV-360 were detected in WWTP effluent and all substances were detected in sludge from WWTPs. However, there were differences both in concentration levels and in distribution among the different benzotriazoles between the WWTPs. A different distribution among the substances was also found in effluent and sludge. Only one sample of WWTP effluent particles was analyzed and only UV-327 was detected in this sample (270 µg/g dw).

Table 29: Concentrations of phenolic benzotriazoles in WWTP effluent and sludge in Sweden

Substance	**effluent WWTP**		**sludge WWTP**	
	detected in x of y samples [x/y]	concentration [ng/L]	detected in x of y samples [x/y]	concentration [µg/g dw]
UV-234	1/5	0.11	8/8	2.1-7.3
UV-320	1/5	4	6/8	0.84-2
UV-327	4/5	0.12-0.48	7/8	0.54-17
UV328	5/5	6.8-15	4/8	2.8-37
UV-329	5/5	0.87-4.9	7/8	2.3-15
UV-360	0/5	-	8/8	4.6-23

All substances but UV-360 were found in landfill leachates, all substances but UV-329 occurred in storm water. In one sample of landfill effluent particles UV-327, -328 and -329 were detected in concentrations of 4.3, 3.1 and 6.1 µg/g dw, respectively.

Table 30: Concentrations of phenolic benzotriazoles in effluent landfill and storm water in Sweden

Substance	**effluent landfill**		**storm water**	
	detected in x of y samples [x/y]	concentration [ng/L]	detected in x of y samples [x/y]	concentration [ng/L]
UV-234	2/3	0.16 and 0.5	4/4	0.06-0.31
UV-320	2/3	7.3 and 23	1/4	0.73
UV-327	2/3	0.45 and 1.3	3/4	0.13-0.17
UV-328	3/3	7-91	3/4	0.19-1.3
UV-329	1/3	17	0/4	-
UV-360	0/3	-	2/4	0.17 and 0.28

In summary widespread occurrence of benzotriazoles in the Swedish environment was observed both in background and urban areas. The substances occurred in all environmental matrices included in the study: air, deposition, surface water, sediment, soil and biota. Diffuse spreading through WWTPs, landfills and storm water may be important for the occurrence in the environment. Levels measured in WWTP effluents and sludge indicate widespread diffusive sources via use of products. The benzotriazoles with the highest usage volume in Sweden (UV-327, UV-328) were also most often found in the highest concentrations.
The authors conclude that on a national scale air transport may be a significant source of the compounds and that the substances are stable enough to undergo atmospheric long range transport.

Carpinteiro et al. (Carpinteiro et al., 2010a) used headspace solid-phase microextraction followed by gas chromatography tandem mass spectrometry for the sensitive determination of benzotriazole UV-stabilizers in water samples (UV-326, -327, -328). The limit of quantification was < 2 ng/l. The developed methodology was used to investigate the presence of benzotriazoles in filtered river water (3 samples), two samples taken in the inlet and outlet streams of an urban WWTP and four additional specimens of raw wastewater provided by a local laboratory. Phenolic benzotriazoles were not detected in river water and treated wastewater. In raw wastewater samples UV-327 was not detected, whereas UV-326 and -328 were each found in 4 of 5 samples in concentrations ranging from 3.5-57 ng/L and 1-19 ng/L, respectively.

Carpinteiro et al. (Carpinteiro et al., 2010b) also investigated benzotriazole UV-stabilizers in indoor dust samples (UV-326, -327 and -328). Pressurized liquid extraction and gas chromatography followed by tandem in time mass spectrometry were used. The limits of quantification were between 4 and 9 ng/g. Procedural blanks showed small peaks at the retention time of some species. The source of this contamination may be related to the trend of target compounds to be retained on solid surfaces. Glass material, extraction cells and connections in the extraction system might contribute to the presence of benzotriazole UV-stabilizers in procedural blanks due to carry over problems.
Dust was collected with domestic vacuum cleaners equipped with paper filter bags from several private houses (5 samples), vehicle cabins (3 samples) and an administrative building (1 sample). It is not stated in which country the dust was collected. However, it was assumed that it was collected in Spain. The dust fraction < 60 µm was used for the study. In addition a house dust reference material from USA was acquired. This sample was used to confirm the ubiquity of benzotriazole UV-stabilizers in dust although no certified or indicative values of their levels in the reference material were available.
UV-326, -327 and -328 were found to be ubiquitous in dust, with measured values from 22 to >600 ng/g. Moreover, UV-326 was found in one car cabin dust sample at a concentration of almost 5 µg/g.

Table 31: Levels of benzotriazole light stabilizers in dust samples (n = 3 replicates) [ng/g]

	UV-326	**UV-327**	**UV-328**
private house 1	42	86	46
private house 2	58	101	127
private house 3	333	29	100
private house 4	73	22	68
private house 5	269	52	149
public building	676	131	62
car cabin 1	4880	48	88
car cabin 2	522	127	124
car cabin 3	170	43	52
US dust reference material	121	322	259
Min-Max (Mean) of all samples except US material	42 – 4883 (780)	22 – 127 (71)	46 – 149 (91)

Carpinteiro et al. (Carpinteiro et al., 2012b) combined stir-bar sorptive extraction and liquid desorption with large volume injection-gas chromatography-mass spectrometry for the determination of benzotriazole UV-stabilizers in wastewater matrices. UV-320, -326, -327 and -328 were measured in urban sewage waters. Grab samples of wastewater were obtained from inlet and outlet streams of two urban WWTPs, equipped with primary and activated sludge treatment units, located in Portugal and Spain. The limits of quantification were between 4 and 10 ng/L. Because of the existence of significant concentrations of phenolic benzotriazoles associated with dust particles it is highly recommended to protect laboratory material from deposition of particulate matter. The efficiency of the extraction is sample dependent; therefore, the standard addition method is required for the accurate quantification of the substances in wastewater matrices.

Table 32: Average concentrations of phenolic benzotriazoles in wastewater matrices (n = 3 replicates) [ng/L]

Place, date	**type**	**UV-320**	**UV-326**	**UV-327**	**UV-328**
Portugal, Nov. 2010	raw wastewater	24	26	85	76
	treated wastewater	n.d.	n.d.	31	21
Spain, Jan. 2011	raw wastewater	n.d.	40 (6)	n.d.	53
	treated wastewater	n.d.	n.d.	n.d.	n.d.
Spain, Feb. 2011	raw wastewater	n.d.	34	22	65
	treated wastewater	n.d.	n.d.	n.d.	n.d.

n.d. = not detected

Carpinteiro et al. (Carpinteiro et al., 2012a) also measured benzotriazole UV-absorbers in sediments. Matrix solid-phase dispersion followed by gas chromatography tandem mass spectrometry was used. The limit of quantification of the method was 3 ng/g for UV-320, -326, -327 and -328. Ten samples of river and estuarine sediments with different carbon contents were investigated. Fresh sediment samples were air-dried in the hood for several days then sieved. The fraction with the particle size < 0.3 mm was considered in the study. In 6 of the 10 sediment samples quantifiable levels of UV-absorbers were detected:

Table 33: Concentrations of benzotriazole UV-absorber species measured in sediment samples (paricle fraction < 0.3 mm, n=3 replicates, - = not detected)

Sample	**total carbon [%]**	**UV-320 [ng/g]**	**UV-326 [ng/g]**	**UV-327 [ng/g]**	**UV-328 [ng/g]**
1	3.0	5.6	32	15	56
2	3.9	-	-	10.3	10
3	5.5	-	7.8	-	8.3
4	4.6	-	-	9.5	11.2
5	2.2	-	-	-	7.9

6	8.0	-	15	-	8

Unfortunately the origin of the sediment samples is not mentioned in the study. According to the acknowledgements some of the analyzed sediment samples were supplied by the German Federal Institute of Hydrology. However, the authors could not specify which samples were from Spain and which were from Germany (personal communication April 2012).

Montesdeoca-Esponda et al. (Montesdeoca-Esponda et al., 2012) used on-line solid-phase extraction coupled to ultra-performance liquid chromatography with tandem mass spectrometry detection (SPE-UPLC-MS/MS) for the determination of UV-326, -327, -328, -329, -360 and -571 in samples from WWTP effluents and coastal marine water from Spain. The detection limits and quantification limits achieved were in the range of 0.6-4.1 ng/L and 2.1-14 ng/L. The analytical method allowed simultaneous determination of the compounds in liquid samples with satisfactory recoveries and reproducibility, except for UV-360, which cannot be completely eluted from the cartridge due to its high octanol-water partition coefficient and molecular mass.
Seawater samples were collected from six beaches around the Gran Canaria Island in Spain (2 samples per beach), wastewater samples were collected from seven WWTPs of Gran Canaria Island. All substances studied were detected in the wastewater samples (see table). In seawater samples only UV-360 was found (6 of 12 samples, 3.6 – 5.2 ng/L).

Table 34: Concentrations of phenolic benzotriazole UV-absorbers in samples of WWTP effluents of Gran Canaria Island

	detection frequency	**concentration(s) [ng/L]**
UV-326	1/7	11
UV-327	1/7	4.8
UV-328	5/7	6.2 – 13
UV-329	1/7	4.0
UV-360	2/7	5.9 and 6.6
UV-571	0/7	not detected

Soil and suspended solids samples from the German Environmental Specimen Bank were analyzed for UV-234, -320, -326, -327, -328, -329 and -350 at the University of Santiago de Compostela (Rodríguez Pereiro and Casado Agrelo, 2012). Samples were extracted using the matrix solid-phase dispersion (MSDP) technique, with an integrated clean-up step. A GC-MS/MS method was used with a hybrid quadrupole time-of-flight mass spectrometer furnished with an electronic impact source. The limits of quantification were 2 ng/g per compound.
Soil samples were from sites with high anthropogenic influence and from background sites. Sampling sites for suspended particulate matter were chosen depending on the contamination with other substances found in previous studies at these sites. Sites with high and low contamination were selected. Five soil samples taken in 2010 and five samples of suspended particulate matter taken in 2011 were analyzed. Soil samples were 3 litter samples, one root network sample and one top soil sample. All soil samples revealed target compound levels below the limits of quantification, also for the soils from Saarbruecken-Staden (root network) and Duebener Heide/Leipzig (litter, top soil) which are assumed to be more anthropogenically influenced. Concentrations of phenolic benzotriazoles in suspended solids samples are shown in Table 35.

Table 35: Concentrations of phenolic benzotriazoles in suspended solids samples from Germany

Suspended solids sample	**UV-234 [ng/g dw]**	**UV-320 [ng/g dw]**	**UV-326 [ng/g dw]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**	**UV-329 [ng/g dw]**	**UV-350 [ng/g dw]**
Danube /	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Jochenstein							
Rhine /Weil	n.d.	n.d.	26	n.d.	26	n.d.	n.d.
Elbe / Cumlosen	8.1	n.d.	4.6	n.d.	n.d.	n.d.	n.d.
Saale / Wettin	15	n.d.	17	n.d.	n.d.	n.d.	n.d.
Saar / Rehlingen	17	n.d.	17	n.d.	n.d.	2.0	n.d.

n.d. = not detected

Suspendid solids from the river Elbe and its tributary Saale showed similar patterns, with higher levels for the tributary Saale. Patterns for suspended solids from the rivers Saale and Saar are comparable. Both rivers revealed high burdens also for other substances. The Rhine site Weil downstream Basel is influenced by the Swiss chemical industry and has a different pattern (higher level of UV 326, only site with UV 328). The Danube site at Jochenstein was selected because of low burdens and displayed levels below the limits of quantification.

Japanese studies:

Nakata et al (Nakata et al., 2009a) studied occurrence and concentrations of UV-320, -326, -327 and -328 in marine organisms and sediments from the Ariake Sea, western Japan. 16 coastal and river sediments were collected during 2006-2007. Five of the sediment samples were taken in a heavily polluted river. 55 biota samples were collected during 2004 and 2007:

- tidal flat organisms: lugworm, lamp shell, oyster, clam, gastropod, crustaceans (crab, shrimp), fishes (herbivorous and omnivorous mudskippers)
- shallow water species: crustaceans (crab, shrimp), teleost fish (flathead, solefish, right eye flounder, sandperch, sweetlips, mullet, sea bass, hairtail), cartilaginous fish (eagle ray, hammerhead shark)
- coastal birds (spot-billed duck, mallard).

Depending on the species, the whole body, soft tissue, hepatopancreas and liver samples were analyzed. 16 coastal and river sediments were also collected around the Ariake Sea during 2006-2007. UV-stabilizers were detected in all biota and sediment samples. In biota UV-326, -327 and -328 were the dominant compounds at levels of 0.1-55 ng/g ww. Concentrations of UV-320 in samples were low, it could be detected only in tidal flat organisms and some shallow water species. This may be due to small amounts of use of this compound in Japan since its domestic production and use have been restricted.
In general, concentrations of UV-stabilizers in tidal flat organisms were greater than those in shallow water species. The average concentrations of UV-320 and UV-326 in tidal flat species were approximately 10- to 20-fold higher than those in shallow water organisms. The tidal flat clam showed the highest concentrations of UV-320 and UV-326 at 74 ng/g and 219 ng/g (lw) respectively. Elevated concentrations of UV-326 were also found in oysters and gastropods in tidal flat area. These results imply the presence of phenolic benzotriazoles in sediment, resulting in accumulation of these compounds in benthic organisms. The low concentrations of UV-326 in shallow water species might be explained by low BCF of this compound, as compared with other benzotriazole UV-filters. In addition the authors speculate that biodegradation of UV-326 in shallow water organisms may be a possible reason for low accumulation of this compound.
UV-327 was most frequently detected in the organisms investigated. The average concentrations of UV-327 in tidal flat organisms were only 2-fold higher than those in shallow water species. The tidal flat clam, crab and herbivorous mudskipper contained high concentrations of UV-327 (> 100 ng/g lw), followed by gastropods and oysters. In shallow water fishes such as mullet, sea bass and young sea bass, concentrations of UV-327 were 3- to 4-fold higher in liver than in carcass. These results are consistent with the concentration profiles of UV-328 in mullet, suggesting the preferential accumulation and less biodegradation of this compound in the liver of some fish species. Omnivorous birds

accumulate UV-327 in the liver, at average concentrations of 90 ng/g (lw) in a spot-billed duck and 59 ng/g in mallards. This suggests bioaccumulation in higher trophic species in the aquatic food chain.
Concentrations of UV-328 in biota were variable and species-specific. The highest concentration was found in tidal flat gastropod at 460 ng/g (lw), followed by mullet (120 ng/g lw in whole body and 250 ng/g lw in liver) and hammerhead shark (130 ng/g lw in liver) collected from shallow waters. The oysters and clams in tidal flat contained high concentrations of UV-328, at >100 ng/g lw. The large variations in UV-328 concentrations observed in this study might be due to differences in retention and metabolism of this compound in marine organisms.
As described above, the concentrations of benzotriazole UV-stabilizers in tidal flat organisms were higher than those in shallow water species. In addition, clams, oysters and gastropods presented high concentrations of UV-320, UV-326 and UV-328 rather than crabs and fishes, although the former species are at lower trophic levels in the tidal flat ecosystems. There is no positive correlation between the concentrations and the trophic status of organisms in marine ecosystems.
The benzotriazole UV-stabilizers were detected in 11 coastal sediments analyzed, at total concentrations of several ng/g dw. UV-328 was found at the highest concentrations (average 6.4± 4.0 ng/g dw), followed by UV-326 (3.7 ± 3.0 ng/g dw), UV-327 (3.2 ± 2.6 ng/g dw) and UV-320 (0.9 ± 0.6 ng/g dw). The composition of the UV-stabilizers among the sediment samples was less variable than in biota. Extremely high concentrations were found in five sediments from the highly polluted Omuta River. Highest concentrations of UV-320, -326, -327 and -328 reached 14, 200, 190 and 320 ng/g dw, respectively. Significant correlations were found in sediment concentrations between UV-326 and 327, UV-326 and 328, and UV-327 and 328 in the Ariake Sea. Significant correlations were also found between UV-stabilizer concentrations and organic carbon contents in sediment.

Table 36: Concentrations of benzotriazole UV-stabilizers in tidal flat and shallow water organisms collected in Japan

	UV-320 [ng/g ww]	**UV-326 [ng/g ww]**	**UV-327 [ng/g ww]**	**UV-328 [ng/g ww]**
10 tidal flat organisms	< 0.05 – 0.60	< 0.10 – 2.5	< 0.12 – 3.6	0.35 - 14
10 marine shallow water organisms	< 0.05 – 0.09	< 0.10 – 0.32	< 0.12 – 2.3	0.19 – 8.7
6 marine shallow water organisms (liver)	< 0.05 – 7.0	< 0.10 – 5.6	2.4 - 13	< 0.15 - 55
2 species of water fowl (liver)	< 0.05	< 0.10	2.6 3.4	< 0.15

Table 37: Concentrations of benzotriazole UV-stabilizers in sediments in Japan

	UV-320 [ng/g dw]	**UV-326 [ng/g dw]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**
marine and estuarine sediments (n = 11)	0.3 – 2.3	1.5 - 12	1.6 – 9.9	7.9 - 40
Omuta River sediments (n = 5)	2.6 - 14	23 – 200	16 – 190	18 - 320

Nakata et al. (Nakata et al., 2009b) also investigated occurrence and concentrations of UV-320, 326, 327 and 328 in marine organisms collected from the Ariake Sea, western Japan. 51 marine organisms, such as lugworms, mussels, oysters, crustaceans, fish, birds and marine mammals were collected during 2001 and 2005. 12 sediments were collected from the same region in 2007. Analyses were done via GC-MS.
UV-filters were detected in most marine organisms in the study. Highest concentrations were found in lower benthic organisms, gastropods, collected from the tidal flat area (UV-328 > 400 ng/g lw). UV-328 and -326 were the dominant components in these organisms. In shallow water species, elevated levels were found in the liver of mullet, a

benthic fish (UV-328 > 200 ng/g lw). Higher trophic species, such as sharks, marine mammals and birds accumulate organic UV-filters. UV-328 and -327 were dominant in finless porpoises and mallards, respectively. The results suggest significant bioaccumulation of UV-filters through the marine food-webs.
The substances were also detected in surface sediments from the Ariake Sea (average concentration: several ng/g dw). High concentrations of UV-filters were found in the Omuta River sediments, at levels ranging from 2.3-320 ng/g dw. Significant correlations were found between concentrations and organic carbon contents in sediments. No more details are given.
In order to understand the geographical distribution of UV-filters, blue and green mussels from 10 Asian countries and regions were collected during 1998 and 2005 and analyzed (Cambodia, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, the Philippines, Vietnam). Only qualitative information is given on this investigation. UV-filters were detected in most mussel samples, indicating the widespread use of these compounds in Asian coastal regions. In general, UV-326 was the dominant compound, whereas UV-320 was detected only in several samples collected from Japan. The UV-filters concentrations were high in mussels from Korea, Japan and Hong Kong. Low residue levels of UV-filters were found in samples from India and Vietnam. These results suggest different usage values of UV-filters among countries and regions in Asia. Concentrations in mussels showed great spatial variations in Korea and Japan, which may be due to the distance between the sampling points and the sources of UV-filters, such as WWTPs. Significant positive correlation was determined in concentrations between UV-327 and UV-328 in mussels.

Nakata and Shinohara (Nakata and Shinohara, 2010) analyzed UV-320, -326, -327 and -328 in influent, effluent and sewage sludge samples collected from 5 WWTPs located in a town (population 680,000) in Japan. Samples were taken in May and October 2009. The wastewater flows were 140,000, 29,300, 9,300, 53,300 and 63,200 m^3/d, respectively. The treatment process included activated sludge method in all WWTPs. In the biggest WWTP (East WWTP) influent samples were collected at 9:00, 12:00, 15:00, 18:00 and 21:00 (n = 5), to study time-dependent variations of target substance concentrations. Influent and effluent samples were also obtained from the 4 other WWTPs (n = 1 / sample). Two sewage sludge samples were also collected from each of the five WWTPs (n = 10). The detection limits ranged from 2.1 to 8.7 ng/L in this study (limits of quantification not given).
Benzotriazole UV-stabilizers were detected in all influents collected from East WWTP at every three hours during 9:00 to 21:00. UV-326 showed the highest concentrations in influents, followed by UV-328 and -327.

Table 38: Concentrations [ng/L] of benzotriazole UV-stabilizers in influents of East WWTP

Time of sampling	**9:00**	**12:00**	**15:00**	**18:00**	**21:00**	**Average ± standard deviation**
UV-326	26	24	23	19	28	24 ± 3.7
UV-327	17	11	10	20	5.6	12 ± 5.6
UV-328	23	20	17	14	15	18 ± 3.9

Table 39: Concentrations of benzotriazole UV-stabilizers in five WWTPs in Japan

Concentration in	**UV-326**	**UV-327**	**UV-328**
influent (9 samples) [ng/L]	24 - 78	< 8.7 - 12	18 - 52
effluent (5 samples) [ng/L]	3.0 - 4.5	< 8.7	2.1 – 2.9
sludge (10 samples) [ng/g dw]	760 - 1800	120 - 200	430 - 570

Benzotriazole UV-stabilizers were detected in most samples analyzed and UV-326 was the dominant compound in influents (mean: 46 ng/L), followed by UV-328 (34 ng/L). UV-327 was detected in two influents at concentrations of 9.2 and 12 ng/L. UV-320 was not identified in any of the samples, probably because its domestic production and use have been restricted in Japan. These results imply a large amount of production and usage of UV-326 compared with other benzotriazole UV-stabilizers in Japan. Concentrations in the effluents were generally < 5 ng/L, suggesting an elimination of these compounds during wastewater treatment. The removal rates of UV-326 and -328 were >90% in the effluents, but high concentrations of benzotriazole UV-stabilizers were detected in sewage sludge samples of WWTPs, at high levels indicating adsorption to organic carbon in sewage sludge. The mean carbon percentage of sewage sludges was 31 ± 2.2 %. Partition coefficients (Kp) were calculated at a moisture content of 80% in sludges. The values are 7,200 ± 3,900 L/kg for UV-326 and 4,200 ± 970 L/kg for UV-328.

Nakata et al. (Nakata et al., 2010) also detected benzotriazole UV-stabilizers in the blubber of marine mammals. They analyzed UV-320, -327 and -328 in finless porpoises (*Neophocaena phocaenoides*) collected from the Yatsushiro Sea, Ariake Sea and Tachibana Bay, Japan, in 1999, 2008 and 2009, respectively. All animals were stranded or accidentally caught by fishing net. Detection limits were 0.05, 0.12, 0.15 ng/g for UV-320, -327 and -328, respectively.

Table 40: Concentrations of benzotriazole UV-stabilzers [ng/g ww] in the blubber of finless porpoises

sample no.	**1**	**2**	**3**	**4**	**5**
sampling year	1999	1999	2008	2009	2009
lipid content [%]	81	83	87	59	91
UV-327	4.5	9.5	6.3	31	18
UV-328	20	64	11	34	16

UV-320 was not detected in the samples, which is attributed to its restriction in Japan in 2007. The mean concentrations and standard deviations of UV-327 and UV-328 in five blubber samples were 19 ± 19 ng/g lw and 38 ± 28 ng/g, respectively, reflecting the higher consumption of UV-328 in Japan.
The authors cite a study showing a high concentration of UV-327 in the liver of a common cormorant (220 ng/g) collected from Hokkaido, northern Japan (respective reference in Japanese). While the concentrations of UV-327 in finless porpoises were lower than those in seabirds, the occurrence of UV-327 in marine mammals suggests the potential bioaccumulation in higher trophic species through the aquatic food chain.
According to the authors it has been reported that UV-327 concentrations in seawater from four coastal areas of Tokyo Bay were less than 0.5 ng/L and that the geometric mean concentration in river, lake and coastal water samples (n = 44) was 0.12 ng/L (respective references in Japanese). On the basis of these water concentrations the BAF of UV-327 between water and finless porpoises was estimated to be 33,300. Applying the same water concentrations to the calculation of a BAF of UV-327 in small fish inhabiting the same regions results in a value of 3250, which is comparable to the values found under laboratory conditions (3400 to 9000).
UV-328 was not detected in the liver of seabirds, although UV-327 was present in the samples (Nakata et al. 2009b). The log K_{ow} of UV-328 is the highest (8.28 reported in study) among the analyzed substances, but the BCF in fish was relatively low, 570-1400 and 620-2700 at the exposure concentrations of 0.1, 0.01 for 60 day, respectively (respective reference in Japanese). However, UV-328 showed a very high BCF, 36,000, between water and innards of fish (respective reference in Japanese). The authors conclude that the bioaccumulation profiles of UV-328 in marine organisms might be related to different retention and metabolism of this compound among species. The occurrence of UV-328 in finless porpoise may imply a low potential for biotransformation of this compound in this species. Finally it is stated that benzotriazole UV-stabilizers appear to be persistent and bioaccumulative in the aquatic food chain.

Kameda et al. (Kameda et al., 2011) measured 18 sun-blocking agents, among them UV-234, -326, -327, -328 and -329 in water and sediment collected from 22 rivers, 4 WWTP effluents and 3 lakes in August and September 2008 in Japan. Phenolic benzotriazoles are the most widely used UV-light stabilizers in Japan. WWTP sediment samples were collected from the river at the point of WWTP effluent discharge. In order to estimate contribution of sun-blocking agents from domestic wastewater to those in surface water and sediment, an indicator chemical for domestic wastewaters and WWTP effluents was also measured (HHCB = 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-[g]-2-benzo-pyrane, a polycyclic musk, CAS 1222-05-5). The sampling sites represent 5 different groups:

- 2 streams with direct inputs of domestic wastewater (S1,S2)
- 4 WWTP effluents (ST1-ST4), conventional activated sludge treatment plants,
- 6 rivers heavily polluted by industrial and domestic wastewaters (H1-H6),
- 12 moderately contaminated rivers (M1-M12),
- 2 little rivers and 3 lakes as background sites (BG1-BG5).

Background sites did not receive domestic or industrial wastewater, but have possible slight sources (atmosphere deposition, recreational activities). In spite of considerable care, UV-328 was detected in blank samples. According to the authors this contamination was caused by analyte in indoor floor dust in the laboratory during experiments. The measured concentrations were corrected by the use of blanks upon each analysis. The limits of detection ranged from 0.1 ng/l to 3.0 ng/l and from 0.05 ng/g dw to 1.0 ng/g dw except for UV-328 which had a LOD of 10 ng/g dw.
The profiles of sun-blocking agents in surface water demonstrated site-specific differences at each sampling site. UV-328 was one of the dominant sun-blocking agents measured in water samples from heavily and moderately polluted rivers. The maximum level of UV-328 in heavily polluted rivers was near the lowest chronic NOEC of the substance estimated by EPI Suite (7 µg/L). UV-234 and UV-329 were neither detected in water samples from surface waters nor from WWTP effluents. At the background sites none of the phenolic benzotriazoles analyzed were found in water samples.

Table 41: Concentrations of phenolic benzotriazoles in water samples. UV-234 and 329 were not detected.

analyte		**UV-326**	**UV-327**	**UV-328**
streams (S1, S2)	Occurrence	1/2	1/2	1/2
	mean detected [a] [ng/L]	16	5	70
	range [ng/L]			
WWTP effluents (ST1-ST4)	Occurrence	1/4	1/4	3/4
	mean detected [ng/L]	13	2	62
	range [ng/L]			47-88
heavily polluted rivers (H1-H6)	Occurrence	1/6	1/6	4/6
	mean detected [ng/L]	9	1	701
	range [ng/L]			149-4780
moderately polluted rivers (M1-M12)	Occurrence	5/12	6/12	8/12
	mean detected [ng/L]	2	1	152
	range [ng/L]	1-22	1-6	30-583
background sites (BG1-BG5)	Occurrence	0/5	0/5	0/5
	mean detected [ng/L]			
	range [ng/L]			

[a] geometric mean calculated from detected samples

Table 42: Concentrations of phenolic benzotriazoles in sediment samples

analyte		**UV-234**	**UV-326**	**UV-327**	**UV-328**	**UV-329**
streams (S1, S2)	Occurrence	1/2	2/2	2/2	2/2	1/2
	mean detected [a] [µg/kg[b]]	1266	7.8	4.7	102	16

	range [µg/kg[b]]		0.1-110	0.6-37	10-1146	
WWTP effluents (ST1-ST4)	Occurrence	0/4	4/4	4/4	3/4	0/4
	mean detected [µg/kg]		0.8	0.5	13	
	range [µg/kg]		0.4-5.4	0.3-1.0	10-85	
heavily polluted rivers (H1-H6)	Occurrence	4/6	5/6	5/6	6/6	3/6
	mean detected [µg/kg]	99	4.7	2.4	117	26
	range [µg/kg]	38-324	0.9-45	0.7-18	21-1735	7.4-269
moderately polluted rivers (M1-M12)	Occurrence	8/12	12/12	10/12	9/12	3/12
	mean detected [µg/kg]	47	1.8	0.9	59	0.6
	range [µg/kg]	18-315	1.0-5.0	0.4-2.6	10-213	0.1-4.3
background sites (BG1-BG5)	Occurrence	3/5	2/5	2/5	3/5	0/5
	mean detected [µg/kg]	39	1.2	0.7	58	
	range [µg/kg]	8.3-113	1.1-1.3	0.5-1.1	29-89	

[a] geometric mean calculated from detected samples
[b] µg/kg dw

UV-234, -326, -327 and -328 were detected in most sediments. The compositions of sun-blocking agents in sediment were quite similar among the five sampling site groups. The highest geometric mean concentrations of 18 sun-blocking agents in sediments were detected in streams and in heavily polluted rivers. The highest contributions to the total concentrations were those of UV-234 and -328. These two substances accounted for 70-80% of the total contaminants identified at all sediment sampling sites.
The results demonstrate that high concentrations of phenolic benzotriazoles were accumulated in sediment receiving not only chemical plants effluent, but also residential wastewaters, WWTP effluent and surface runoff.
UV-234, -326, -327 and -328 were significantly correlated with HHCB in sediments from rivers and lakes. According to the authors this shows that a large input of these substances is from domestic wastewater or WWTPs. It also suggests that their behavior in rivers and lakes, such as partitioning and attenuation, is similar to that of HHCB. UV-329 had no significant correlation with HHCB in sediments.
UV-326 had a strong linear correlation between UV-327 as well as UV-328 in all sediments. Since UV-stabilizers are often used as mixtures, the ratios observed in sediments may reflect their compositions in the products. The authors suggest that their (degradation) behavior may be also quite similar.

In a presentation Nakata (Nakata, 2011) showed graphs with concentrations of UV-326, -327 and -328 in mussels from 10 Asian countries and in mussels from the USA mussel watch program. All data cited are taken from the graphs. 45 samples were taken during 2003 and 2005.
UV-326 was detected in mussels from 7 of the 10 Asian countries. Highest concentrations were detected in mussels from Japan and Korea (ca. 1.5 and ca. 1.2 µg/g lw, respectively). UV-327 was detected in 6 of the 10 countries with highest concentrations in Hong Kong and Korea (ca. 0.3 µg/g lw). UV-328 was detected in 8 of the 10 countries with highest concentrations in Hong Kong and Korea (ca. 0.8 µg/g lw).
In the USA samples were taken from blue mussels at 17 locations (n = 34) on the west coast (Alaska, Oregon, California) in 1994/95 and 2004/05. UV-326 and -327 were detected in most samples (14/17). Concentrations of UV-326 were similar to those measured in Japan and Korea. However, the maximum concentration was lower (ca. 0.7 µg/g lw). Concentrations of UV-327 were higher than in Japan, but slightly lower than in Korea and had a maximum of ca. 0.25 µg/g lw. UV-328 was detected in few samples, only, and showed a maximum of ca. 0.3 µg/g lw.
In an article Nakata et al. (Nakata et al., 2012) published more details on the mussel analyses. However, some more samples were included and other samples were excluded, so the results published in the article differ somewhat from those given in the presentation. Compounds analyzed were UV-320, -326, -327 and -328. 53 samples of blue and green mussels were collected from Cambodia, China, Hong Kong, India,

Indonesia, Japan, Korea, Malaysia, Philippines and Vietnam during 2003 and 2007. In addition the analysis comprised 15 samples of blue mussels from the Pacific coast of the USA collected during 2004 and 2005. Liquid extraction and GC-MS in selective ion monitoring (SIM) mode was used. The limits of detection are given as 0.05, 0.1, 0.12 and 0.15 ng/g ww for UV-320, -326, -327 and -328, respectively.

Table 43: Mean concentrations of phenolic benzotriazoles in blue and green mussels [ng/g lw]. Geometric means in parenthesis.

	UV-320		**UV-326**		**UV-327**		**UV-328**	
Cambodia	0/2	n.d.	0/2	n.d.	0/2	n.d.	2/2	120 (110)
China	0/5	n.d.	2/5	60 (33)	4/5	84 (65)	3/5	96 (52)
Hong Kong	0/8	n.d.	2/8	91 (18)	6/8	93 (48)	6/8	200 (75)
India	0/3	n.d.	0/3	n.d.	0/3	n.d.	0/3	n.d.
Indonesia	0/2	n.d.	1/2	33 (22)	2/2	58 (45)	2/2	120 (110)
Japan	4/7	33 (13)	7/7	450 (260)	3/7	38 (15)	7/7	120 (93)
Korea	0/17	n.d.	13/17	210 (90)	11/17	100 (56)	16/17	220 (150)
Malaysia	0/4	n.d.	1/4	42 (12)	0/4	n.d.	1/4	24 (14)
Philippines	0/2	n.d.	1/2	120 (50)	2/2	150 (150)	2/2	170 (140)
USA	0/15	n.d.	12/15	130 (79)	11/15	61 (45)	3/15	69 (33)
Vietnam	0/3	n.d.	0/3	n.d.	0/3	n.d.	0/3	n.d.

Analytical results demonstrate ubiquitous contamination and widespread distribution of phenolic benzotriazoles. Levels were comparable to those of PCBs, DDTs and PBDEs. However, spatial variation of the concentrations was often high. Significant correlations were found between the concentrations of several phenolic benzotriazoles, which suggests similar sources and compositions of these compounds in commercial and industrial products. While Kameda et al. (2011) reported correlations of UV-326, -327 and -328 with the polycyclic musk HHCB, such correlations were not always found by Nakata et al. (2012). HHCB is an indicator substance for WWTP effluent. It is concluded that in addition to WWTP effluents there may be point sources or other sources, e.g. road dust, influencing the phenolic benzotriazoles concentrations in mussels.
The authors report that the domestic production and import of UV-327 in Japan decreased dramatically from 2436 tons between 2004 and 2009 to only 3 tons in 2010. They assume that this is due to the availability of an alternative in the Japanese market.
Yanagimoto et al. (Yanagimoto et al., 2011) studied the occurrence of UV-327 and -328 in human adipose tissues collected from Japan (2004-2005, n = 22), South Korea (2005-2006, n = 18), China (2002, n = 12), India (2008, n = 5), Spain (2006, n = 12), Poland (1990, n = 12) and the USA (2003-2004, n = 24). In addition foodstuffs collected from Japan were analyzed for UV-326, -327 and -328 (seafood, meat, eggs, vegetables, dairy products, potatoes, pulses, cereals, fruits, n = 32). Some of the foodstuffs originated from other countries than Japan. GC-HRMS/LRMS was used. All data cited are taken from graphs.
The highest concentrations in human adipose tissue were found In Japan and South Korea. In Japan up to ca. 60 ng/g lw UV-327 were detected in human adipose tissues, in South Korea the concentrations reached ca. 45 ng/g, whereas those in Europe were lower (up to ca. 17 ng/g in Spain, up to ca. 11 ng/g in Poland). Lowest concentrations were observed in the USA (up to ca. 5 ng/g lw). Concentrations of UV-328 were generally lower than those of UV-327: up to ca. 35 ng/g lw in Japan, up to ca. 20 ng/g in South Korea and up to ca. 6 ng/g in Spain, whereas UV-328 was not detected in samples from Poland and only in few samples at low concentrations in the USA (up to ca. 2 ng/g lw). No gender- and age-related differences in concentrations were observed.
In foodstuffs ubiquitous contamination with benzotriazole UV-stabilizers was found. Highest concentrations were detected in seafood (up to ca. 1.2 ng/g ww UV-326, 1.4 ng/g UV-327 and 1.7 ng/g UV-328) and meat (up to ca. 1.5 ng/g ww UV-326, 1.2 ng/g UV-327 and 1.0 ng/g UV-328). Meat with high concentrations was imported from the USA and Australia. Lower concentrations were detected in vegetables (up to ca. 1.0 ng/g

ww UV-326, 0.3 ng/g UV-327 and 0.2 ng/g UV-328) and some fruit (up to ca. 0.5 ng/g ww each UV-326, 327 and 328). In dairy products no benzotriazole UV-stabilizers were found. The estimated daily intake of benzotriazole UV-stabilizers through food consumption was 861 ng/person/d. Contamination was mainly due to meat and vegetables (> 50%), which may imply the transfer of benzotriazole UV-stabilizers from plastic trays and wraps.

By way of a poster Nakata et al. (Nakata et al., 2011) reported temporal trends of UV-327 and -328 in archived marine mammal tissues. In addition temporal trends of UV-326, -327 and -328 in sediment cores were analyzed. Marine mammals sampled were finless porpoises and striped dolphins from Japanese coastal waters (n = 33). Sediment cores were taken from two sample stations at Tokyo Bay, Japan (n = 12). The sedimentation periods (1930-1999) were determined by ^{210}Pb and the particle fraction < 500 µm was investigated. All data cited are taken from graphs.

UV-327 and -328 were not detected in blubber samples collected around 1980, but in samples taken in 1990 and later. Maximum concentrations of UV-327 and -328 were ca. 45 ng/g lw and ca. 70 ng/g lw, respectively. An increasing trend is identified for UV-327 as well as UV-328.

Sediment cores showed an increasing temporal trend for UV-326, -327 and -328. Results are presented for two different sampling stations. At both sampling stations concentrations start to rise around 1970. Highest concentrations are found for UV-326 (maximum ca. 17 ng/g dw at station A, ca. 31 ng/g at station B), whereas concentrations of UV-327 and -328 were lower (UV-327 maximum ca. 8 ng/g dw at station A, ca. 4 ng/g at station B, UV-328 ca.10 ng/g at station A, ca. 4 ng/g at station B).

UV-320, -326, -327 and -328 were also detected in road dusts. Samples were collected in December 2010 at 9 stations of Route 57, Kumamoto, with a traffic density of approx. 5,000 to 60.000/d (Nakata Presentation, 2011). All data are taken from graphs.

Concentrations were low for UV-320 (n.d. - ca. 3 ng/g dw), higher for UV-328 (ca.2.5 - ca. 40 ng/g) and UV-326 (ca. 8 - ca. 55 ng/g) and at a single sampling point 116.9 ng/g UV-327 was detected (minimum ca. 8 ng/g dw). Concentrations of UV-320, -326 and -328 correlated with traffic density. The authors conclude that that automobile equipment might be a possible source of benzotriazole stabilizers in the environment.
Based on the data set obtained and the physicochemical properties of benzotriazole UV-stabilizers, the authors conclude that UV-327 will be a candidate of the POP Convention.
Watanabe and Noma (Watanabe and Noma, 2010) performed thermal treatment experiments using pilot-scale equipment and waste containing UV-320 as an input material to determine the destruction behavior of UV-320 and possible formation of UV-327 and NOx.

UV-320 was classified as a "Class I Specified Chemical Substance" under the Chemical Substance Control Law in Japan in 2007, which means that it is comparable in nature and toxicity to POPs (Watanabe and Noma, 2010). Manufacture and import of this substance have to be permitted, only specified uses are allowed and import of certain products specified by cabinet orders is prohibited. Therefore production, import and use of UV-320 have declined in Japan. However, it is still used in some countries, such as Korea and China and in Japan it may still be leached from long-life products. It is expected that incineration may be the predominant method of treatment for wastes containing UV-320.
Concentrations of UV-320 and -327 in "refuse derived fuels" obtained from Japanese municipal solid waste after removing the incombustible materials were 7.1 and 20 µg/kg, respectively. After treatment in the pilot-scale incinerator with two combustion units, bag filter, activated carbon adsorption tower and wet scrubber concentrations in the flue gas (final exit) were 0.0020 µg/m³ and 0.0042 µg/m³ for UV-320 and -327, respectively.

Bottom ash contained 0.52 µg/kg UV-320 and 0.063 µg/kg UV-327, fly ash 0.36 µg/kg UV-320 and 0.049 µg/kg UV-327. After increasing the input concentration to 5000 mg/kg UV-320 concentrations of UV-320 and 327 in flue gas, bottom ash and fly ash were of the same order of magnitude as those observed at low input concentrations of UV-320.

UV-320 was destroyed mainly in the primary combustion zone. Overall destruction efficiency of UV-320 in input at a concentration of 5000 mg/kg was > 99.9999%. The input amount of UV-320 did not affect the formation and destruction behavior of UV-327 and NOx.

Other Asian studies:

Kim et al. (Kim et al., 2011b) developed a multiresidue analytical method for the determination of emerging pollutants including UV-234, -320, -326, -327, -328 and -329 in fish. The concentrations in fish muscle tissue were given on a lipid weight (lw) basis and the method detection limits were 0.3 – 9 pg/g for the UV-stabilizers mentioned above. Five individual fish samples belonging to three species of fish from Manila Bay, the Philippines were analyzed. Samples were collected during June 2008. Concentrations ranged from < method detection limit to 179 ng/g lw, suggesting the ubiquitous contamination in Manila Bay.

Table 44: Concentrations of phenolic benzotriazoles in fish muscle tissue [ng/g lw]

	bluetail mullet *V. buchanani* (n=1)	**coral grouper *E. corallicola* (n=1)**	**flathead grey mullet *M. cephalus* (n=3)**	
			mean	Min-Max
UV-234	not detected	14.3	34.6	22-47.1
UV-320	9.60	0.78	6.88	4.11-9.15
UV-326	211	n.d.	18.9	no data given
UV-327	2.57	18.5	14.6	10.5-18.5
UV-328	18.4	21.1	105	30.2-179
UV-329	not detected	39.4	7.29	6.69-7.89

Using the same method Kim et al. (Kim et al., 2011c) studied contamination of fish from Manila Bay, the Philippines, with benzotriazole UV-stabilizers including UV-234, -320, -326, -327, -328 and -329. Manila Bay is one of the pollution hot spots in the seas of East Asia with a very dense population and significant fisheries and aquaculture activities. It serves as a sink and transit area for the domestic and industrial wastes from metro Manila and the surrounding provinces. Many people depend on fish from the bay for food. During January and June 2008 58 fish specimens belonging to 20 species were collected from the local fish markets. Only fishes from Manila Bay were selected and analyzed. The method quantification limits were 1-27 pg/g lw.
Benzotriazole UV-stabilizers were detected, each at ng/g level in almost all fish samples, indicating ubiquitous contamination in coastal waters. Among the 8 targeted substances UV-328 was predominantly found with a mean concentration of 34.2 ng/g lw, implying large scale production and use of this compound in the Philippines. UV-328 was found in 88% of analyzed specimens (n = 58), UV-320 and UV-234 in 79% and 55%, respectively. UV-326, -327 and -329 were detected in less than half of the samples suggesting smaller amount of use or lower bioavailability. Generally concentrations of UV-320, -326, -327 and -328 in fish samples from the Philippines were higher than those reported in marine fish from shallow waters of Japan (Nakata et al., 2009a), which is attributed to large scale usage of the substances and/or the release of untreated wastewater containing the substances. In line with the results of Nakata et al. (2009a) concentrations of UV-320, though frequently detected, were lower than that of UV-234 and -328. According to the authors this may indicate the differences in accumulation and biodegradability of UV-320. Significant positive correlations were found between UV-234 and -328, UV-234 and -329, UV-320 and -327 and UV-320 and UV-328. From this it is

suggested that fish in Manila Bay are exposed to benzotriazole UV-stabilizers originating from the same sources which are distributed homogenously in the bay. Examination of the relative contributions of each analyte to the total concentrations of analytes revealed that from the substances relevant for the SVHC dossier UV-328 was predominant. Compositions of the benzotriazole UV-stabilizers were different even in fishes belonging to the same family whereas some composition pattern was observed in fishes belonging to different families. This may be due to different availability, different metabolic capacity or selective uptake of the substances.
Concentrations of UV-234, -320, -326, -327, -328 and -329 did not show any relation with fish length and weight. Therefore, differences in accumulation/exposure pattern indicate the species specificity in fish samples. Concentrations measured in the different fish species varied greatly depending on the species within one to two orders of magnitude. This wide variation in concentrations indicates species-specific accumulation and elimination of the substances.
High concentrations of the sum of the investigated 8 substances were found in bumpnose trevally (*Caranoides hedlandensis*, n = 3), bluetail mullet (adult) (*Valamugil buchanani*, n = 1), common ponyfish (*Leiognathus equulus*, n = 3) and coral grouper (adult) (*Ephinephelus corallicola*, n = 1). These high concentrations (several hundred ng/g lw) indicate that these compounds are preferably accumulated by these species and/or that these species may have low metabolic capacity to eliminate benzotriazole UV-stabilizers. All these fishes belong to the demersal habitat.

Table 45: Concentrations of benzotriazole UV-stabilizers in marine species from Manila Bay, the Philippines

	lipid content [%]	**UV-234 [ng/g lw]**	**UV-320 [ng/g lw]**	**UV-326 [ng/g lw]**	**UV-327 [ng/g lw]**	**UV-328 [ng/g lw]**	**UV-329 [ng/g lw]**	**Σ 8 benzotriazole UV-stabilizers**
detection frequency [%]	**---**	55	79	19	43	88	41	**---**
Min. – Max. in 20 fish species (n = 58)	0.13-2.61	n.d. - 126	n.d. – 28.7	n.d. - 211	n.d. - 221	n.d. - 563	n.d. - 96.7	6.5 ± 11.1 - 316 ± 460

Kim et al. (Kim et al., 2012) used the same method for determining UV-234, -320, -326, -327 and -328 in house dust from the Philippines. During August 2008 house dust samples were collected from a residential area (Malate, n = 17) and near a large-scale open dumping area of municipal wastes (Payatas, n = 20) in Manila. People live directly at and even on the dumping area (http://www.dr-koelsch.de/html/payatas.html). House dust was collected in separate vacuum-cleaner bags used in each of the sampled house, which consist of dust from living room, kitchen and bedrooms. Dust was not collected from under furniture or in crevices between cushions. Obtained dust samples were combined individually for each house and sieved with a 500 µm mesh. Data on the details of the house, the possible sources of dust, floor area, number of computers/televisions, furniture and type of flooring were documented in a questionnaire at the time of sample collection.

Table 46: Concentrations of benzotriazole UV-stabilizers in house dust samples from Malate and Payatas in the Philippines

Target compounds	**Malate**					**Payatas**				
	DF[a] [%]	**Median [ng/g]**	**Average [ng/g]**	**Min. [ng/g]**	**Max. [ng/g]**	**DF[a] [%]**	**Median [ng/g]**	**Average [ng/g]**	**Min. [ng/g]**	**Max. [ng/g]**
UV-234	94	84	148	n.d.[b]	817	95	41	63	n.d.	212
UV-320	82	4.7	6.6	n.d.	25	65	3.0	6.9	n.d.	75

UV-326	88	50	53	n.d.	275	65	6.2	17	n.d.	133
UV-327	88	19	28	n.d.	73	80	10	10	n.d.	32
UV-328	82	27	50	n.d.	304	85	12	18	n.d.	48
Σ	**---**	147	285	n.d.	1020	**---**	118	115	n.d.	277

[a] DF: detection frequency
[b] n.d. = not detected

UV-234, -320, -326, -327 and -328 were frequently detected indicating ubiquitous contamination of the indoor environments. Among the target compounds, UV-234, -326 and -328 were the predominant compounds. The most abundant was UV-234, with a median value of 84 ng/g in Malate and 41 ng/g in Payatas. Significantly higher concentrations of UV-326 and -327 were found in house dust samples from Malate than those from Payatas, indicating possible differences in usage patterns of household products such as TV, waxes, coating materials, paints etc. between the two locations. Household products are considered the major source of contamination in the indoor microenvironment. The composition of phenolic benzotriazoles differed among the houses even within the same sampling region. It was not possible to distinguish the sources of the contamination. However, the correlations found for most of the benzotriazole UV-stabiliszers in house dust samples indicate a common source. This is in line with the results from other investigations (Kim et al.2011a, Nakata et al. 2009a)
Generally, levels of benzotriazole UV-stabilizers in dust from the Philippines are comparable to or lower than those measured by Carpinteiro et al. (2010b) in dust from Spain or the USA. Lower levels are attributed to lesser usage of the respective compounds in the Philipines.
Zhang et al. (Zhang et al., 2011) investigated UV-326, UV-327 and UV-328 in surface sediment samples (0-20 cm) collected from rivers in China (6 samples from river Songhua in 2009) and the U.S. (3 samples both from river Saginaw in 2002 and river Detroit in 1998). Five sewage sludge samples were collected from five WWTPs serving large cities located along the Songhua River in China in July 2009. Sediment and sludge samples taken from 4-6 spots within 10 m at a given sampling location were pooled to obtain a representative sample. UV-326, UV-327 and UV-328 were determined by use of a GC-MS.
The limit of detection (LOD) and the limit of quantification (LOQ) for sediment analysed in this study were 0.02 and 0.06 ng/g for UV-327 and 0.1 and 0.33 ng/g for both UV-326 and UV-328.The method LOD and LOQ values for sludge samples were 0.1 and 0.3 ng/g for UV-327 and 0.5 and 1.65 ng/g for both UV-326 and UV-328.
UV-326 was detected in 2 of 6 sediment samples from the Chinese River (1.71 and 2.01 ng/g dw) in 1 of 6 sediment samples from the U.S. (5.88 ng/g dw) and in all 5 sewage sludge samples from China (23.3-136 ng/g dw, mean 77.4 ng/g dw).
UV-327 was detected in 1 of 6 sediment samples from the Chinese River (0.310 ng/g dw) in 3 of 6 sediment samples from the U.S. (0.22-1.90 ng/g dw, mean 0.850 ng/g dw) and in 4 of 5 sewage sludge samples from China (1.80-8.40 ng/g dw, mean 3.68 ng/g dw).
UV-328 was detected in all 6 sediment samples from the Chinese River (2.06 - 7.12 ng/g dw, mean 3.81 ng/g dw) in 5 of 6 sediment samples from the U.S. (0.72-224 ng/g dw, mean 116 ng/g dw) and in all 5 sewage sludge samples from China (40.6-5920 ng/g dw, mean 1300 ng/g dw).
The concentration of UV-328 in sludge was the highest (mean: 1300 ng/g dw) among the target compounds.
Ruan et al. (Ruan et al., 2012) analyzed UV-234, -320, -326, -327, -328, -329 and -350 in municipal sewage sludge in China using an HPLC-MS/MS method. The method quantification limits were from 0.15 (UV-234) to 0.77 (UV-320) ng/g dw. Sixty sewage sludge samples from WWTPs in 33 cities were collected in 2010 and 2011. Most of the WWTPs are located in economically developed provinces in China. Samples were taken from freshly digested sludge at the dewatering process. The most dominant analogue was UV-234 at a median concentration of 116 ng/g dw. The abundance was successively followed by UV-329, -326 and -328 with median concentrations of 66.8, 67.8 and 57.3

ng/g dw respectively. UV-327 and UV-350 had low detection frequency, while UV-320 was not detectable in any sample. According to the authors the observed composition pattern in the sludge samples was quite consistent with the global production volumes of benzotriazole UV-stabilizers (according to the OECD and US EPA HPV databases).
Significant correlations were found among the phenolic benzotriazole concentrations and the daily treatment volume of the WWTPs was moderately correlated UV-329 and UV-328. Results from degradation prediction and multimedia fate simulation based on a quantitative structure-property-relationship (QSPR) model at screening level based on EPISuite and therefore comparable with the simulations done for the presented dossiers implied that the commercial benzotriazole stabilizers and their plausible transformation products might be persistent in the environment.

Table 47: Concentrations of benzotriazole UV-stabilizers in sludge from Chinese municipal WWTPs

Analyte	Detection frequency	Concentrations [ng/g dw]	Median [ng/g dw]
UV-234	58/60	0.96 – 235	116
UV-320	0/60	n.d.	-
UV-326	59/60	4.00 – 319 two extreme values: 2930 and 3390	67.8
UV-327	24/60	1.53 – 133	14
UV-328	58/60	3.54 – 213 one extreme value: 24,700	20.6
UV-329	59/60	0.57 – 757	66.8
UV-350	5/60	1.88 – 42.7	13.8

Australian studies:
Liu et al. (Liu et al., 2011b; Liu et al., 2012) developed a method for simultaneous determination of benzotriazoles and UV-filters (including UV-326 and -329) in ground water and WWTP effluent and biosolid samples using GC-MS/MS. The method was applied to screen the selected substances in samples from Bolivar WWTP in Adelaide, South Australia. The WWTP serves a population of 1,300,000 and is designed to have dry weather flow of 148.5 ML/d. About 75% of the inflow is from domestic sources, 25 % from industrial sources. The WWTP consists of primary sedimentation, secondary activated sludge treatment, stabilization lagoons and dissolved air flotation/filtration. The effluent is piped to a vegetable growing region for irrigation, or recharged into aquifer on site. The sludge line comprises mesophilic anaerobic digestion and sludge stabilization lagoons.
Groundwater samples were collected from an aquifer storage and recovery well at a depth of 300 m below ground within the WWTP site. Biosolid samples were collected from different sludge treated process (sludge is dewatered and dried using a combination of sludge drying lagoons, centrifugation and agitated air drying). 3 parallel samples were collected for each sample type.
In groundwater and effluent water concentrations of UV-326 and -329 were below the limits of quantification (LOQ). The LOQ were: 4.9 ng/L in tap water and 11.0 ng/L in effluent for UV-326 and 18.6 ng/L in tap water and 16.0 ng/L in effluent for UV-329. The concentration in biosolid samples was 49.9±7.4 ng/g for UV-326 (LOQ 1.1 ng/g) and 122.9±7.1 ng/g for UV-329 (LOQ 27.4 ng/g).
Results published in 2012 focus on the removal processes in the WWTP. 24 h composite water samples and samples of sludge (24 h composite or grab) and influent suspended solids were collected in April and October 2010. The average removal efficiencies of suspended solids, BOD_5 and NH_4-N were above 99% during the sampling periods. The highest value of LOD for the target analytes (4 benzotriazoles and 6 UV-filters including UV-326 and -329), were 16.3 ng/L in the influent, 14.1 ng/L in the effluent and 8.2 ng/g in biosolid samples.
All water and sludge concentrations are taken from graphs. UV-326 was detected in the influent in concentrations of ca. 35 ng/L (April) and ca. 20 ng/L (October), UV-329 in

concentrations of ca. 230 ng/L (April) and ca. 420 ng/L (October). According to the authors both substances were completely removed from the water phase. However, removal rates of both > 100% and < 0% were noticed in some treatment stages, which might be due to variations in the input and output concentrations. Concentrations of UV-326 and UV-329 in influent suspended solids were always near 100 ng/g. Both substances are further detected in all other sludge samples taken after different treatment steps.
A mass balance analysis was applied to establish mass flux in the plant and removal mechanisms. However, few data were available, concentrations in water and sludge varied considerably with different treatment stages. The authors discuss plenty uncertainties associated with the mass balance analysis, but nevertheless state that sorption onto sludge played a dominant role in the removal of UV-326 in the WWTP whereas biological degradation played a significant role for UV-329.

American studies investigating the environmental impact of a certain industrial point source:

Jungclaus et al. (Jungclaus et al., 1978) analyzed industrial WWTP effluent and receiving waters and sediments from an American specialty chemicals manufacturing plant producing organic compounds and running a badly performing WWTP. 16 water samples and 19 sediment samples were taken in 1975 and 1976 and the compounds contained were identified, beside others UV-320, -327 and -328. River water and sediments were collected in Providence River and its tributary Pawtuxet River (Pruell et al., 1984).
UV-328 was detected in industrial WWTP effluent (0.55 – 4.7 ppm), in river water (7 – 85 ppb) and in sediments (1-100 ppm). UV-320 and UV-327 were detected only in sediment, with concentrations of 40 ppm and 2 – 300 ppm, respectively.

Lopez-Avila and Hites (Lopez-Avila and Hites, 1980) investigated transport of pollutants in sediments in the USA. The wastewater from a small specialty chemicals manufacturing plant located on the Pawtuxet River (Rhode Island) contaminated the water and sediment of that river, which flows into the brackish Providence River and Narragansett Bay. UV-328 had been manufactured in the plant since 1970. Wastewater samples from the clarifier tank, water samples and sediment cores were taken. Reported concentrations represent minimum values since they had not been corrected for solvent extraction efficiencies. Average water concentrations for UV-328 (geometric averages of 2-5 values measured at the specified locations at different times) were 3000 ppb in the wastewater of the plant, 40 ppb in river water near the plant, 10 ppb in more distant river water, 8-9 ppb in the mouth of the Pawtuxet River and 0.5-2 ppb in the Providence River. The concentrations follow the rules of simple dilution. UV-327 was manufactured at the plant between 1963 and 1972. It was not detected in any of the water samples.
Eight sediment cores were taken at three locations in the Pawtuxet River. The sites were selected for an abundance of fine-grained material. Further sediment cores were taken at 4 locations in the Pawtuxet Cove and 13 locations in the Providence River and Narragansett Bay. The core concentrations of the compounds in the sediment have been condensed into a single number. However, the authors feel the values given are representative of the sediment concentrations. Concentrations decrease both with depth in the sediment and with increasing distance from the discharge.

Table 48: Concentrations of phenolic benzotriazoles in sediment cores (ppm)

	Pawtuxet River			**Pawtuxet Cove**	**Providence River**		
	near plant	**mid river**	**near dam**		**near**	**far**	**bay**
UV-327	300	400	20	80	20	2	0.5
UV-328	300	300	70	100	10	5	0.6

Pruell et al. (Pruell et al., 1984) developed an analytical method for the determination of PAHs and phenolic benzotriazoles in clams. Concentrations of UV-327 and -328 were measured in hard shell clams (*Mercenaria mercenaria*) purchased from Rhode Island

seafood stores in 1979. Personnel in nine of the 13 stores surveyed indicated that the clams were harvested from Narragansett Bay. Three seafood stores were sampled a second time to determine if the higher values obtained at these establishments were representative of their usual stock. As controls, clams were collected from a relatively unpolluted site in lower Narragansett Bay. The detection limit for specific compounds was ca. 0.1 ng/g ww.
The levels in purchased clams were generally higher than the concentrations found in clams collected from a lower Narragansett Bay control location. However, also in control samples both substances were detected. In summary UV-328 and UV-327 were present in clam tissue in concentrations ranging from 7 – 65 ng/g ww and from 1.0 – 8.5 ng/g ww (including controls). The ratio of UV-328 to UV-327 in clams varied from 2.7 to 9.5. This is similar to the ratio in surface sediments of the bay which ranges from 2.0 to 7.6. A significant correlation existed between UV-327 and UV-328.

Reddy et al. (Reddy et al., 2000) examined the free and bound fractions of different substituted benzotriazoles in sediment cores from the Pawtuxet River and Narragansett Bay in the U.S. The chosen benzotriazoles were produced from 1961 to 1985 by a major chemical plant located on the Pawtuxet River. Beside others, UV-326, -327 and -328 were investigated. Previous research has used these compounds as specific tracers of inputs from the Pawtuxet River into Narragansett Bay sediments and they are highly enriched in the sediments of both.
The Pawtuxet River sediment core was collected in 1989 and sectioned at 2-3 cm intervals. Eleven sections from 0-2 cm to 50-52 cm were analyzed. The sedimentation rates in this section of the river are 2-3 cm/year. The redox discontinuity, determined visually, was in the top 2 cm of the core. The Narragansett Bay core was collected in 1997. Six sections from the top 13 cm of the core were analyzed. The sediments in this area become anoxic within a few millimeters of the surface and have a sedimentation rate of about 0.3 cm/year. The deepest sections of both cores were the approximate depths of where the phenolic benzotriazoles were no longer detected and should roughly be equivalent to the initial date of production of these compounds (1961-1979). The method detection limit was ca. 20 ng/g for each (free and bound) fraction.
In the Narragansett Bay core UV-327 and -328 were detected at trace levels in the 10-13 cm section and their concentrations generally increased up-core (with concentrations as high as 25 µg/g). UV-326 was detected at much lower concentrations. UV-327 and -328 were not detected in the bound fraction in the Narragansett Bay core.
In the Pawtuxet River core all benzotriazoles were detected in the free fraction. UV-327 was most abundant: the highest concentration was ca. 5 mg/g and it was observed down to 50-52 cm. The other benzotriazoles were only present in the top 20 cm of the core. UV-326 and -327 were also found in the bound fraction of the Pawtuxet River core in at least the top 15 cm. However, the maximum percentage bound was 0.04%.
Benzotriazoles that had alkyl substitution in ortho position to the hydroxyl group were less likely to be found in the operationally defined bound fraction than compounds that did not have this substitution.

Hartmann et al. (2005) took sediment cores at three locations in Narragansett Bay in 1997 (Apponaug Cove, Seekonk River, Quonset Point). The cores were analyzed for several contaminants including UV-327 and UV-328. The phenolic benzotriazoles were used as markers indicating the years of their introduction (1963 for UV-327 and 1970 for UV-328). Two of the cores were split into 2 cm sections, and the third core (Quonset Point) was split into 10 cm sections.

Sharp breaks in the concentrations of UV-327 and UV-328 marking their introduction were successfully used to determine the sedimentation rate at Quonset Point. Both the Quonset Point and Seekonk River cores had subsurface maximums for phenolic benzotriazoles, which were consistent with expected inputs to the environment. The Apponaug Cove core showed an increase of the contaminants at the surface indicating a

recent event in which more contaminated sediments were deposited at that location. The distributions of phenolic benzotriazoles at Apponaug Cove and in the Seekonk River indicate that there was a disturbance in the depositional environment relative to cores collected at these locations in 1986, demonstrating the potential for buried contaminants to be remobilized in the environment even after a period of burial.

At Quonset Point the phenolic benzotriazole profile increased down core through the 40-50 cm section before decreasing in the 50-60 cm section. Below the 50-60 cm section, UV-327 and UV-328 were below the detection limit of 10 ng/g dw. In the 50-60 cm section UV-327 is much more prominent than UV-328. Moving up core, UV-328 progressively accounts for more of the sum of both phenolic benzotriazoles. This reflects the earlier introduction (1963) and subsequent earlier discontinuation (1972) of UV-327 relative to UV-328 (1970 and 1985, respectively).

At Apponaug Cove surface concentrations were higher than the lower sections of the core. There could be degradation in the oxic surface layer of the sediments with subsequently lower concentrations in the deeper sections. However, data from a core taken in 1986 had a profile more consistent with the appearance of the different analytes. Therefore the authors assume that the distribution of phenolic benzotriazoles represents resuspended sediment transport and deposition of materials with high concentrations.

Data from the Seekonk River core also show high concentrations in the surface layer. Another core taken in the same area in 1986 showed a more orderly decrease down to 70 – 80 cm. The authors assume that some sedimentary layers were removed. Additional evidence of a disturbance is found in the ratio of the phenolic benzotriazoles. The lowest core section with phenolic benzotriazoles (12 – 14 cm) should have high ration of UV-327 to UV-328 due to their production history, but in this case actually had a lower ratio of UV-327 to UV 328 than the sections above it.

Table 49: Concentrations of phenolic benzotriazoles in sediment cores from Narragansett Bay (concentrations taken from a graph)

Quonset Point core			**Apponaug Cove core**			**Seekonk River core**	
depth [cm]	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**	**depth [cm]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**	**UV-327 [ng/g dw]**	**UV-328 [ng/g dw]**
0 - 2	ca. 40	ca. 160	0 - 2	ca. 130	ca. 270	ca. 30	ca. 120
0 - 10	ca. 60	ca. 260	2 - 4	ca. 30	ca. 80	ca. 20	ca. 70
10 - 20	ca. 80	ca. 360	6 - 8	ca. 50	ca. 140	ca. 30	ca. 140
20 - 30	ca. 100	ca. 840	10 – 12	ca. 70	ca. 120	-	-
30 - 40	ca. 130	ca. 1100	12 - 14	-	-	ca. 5	ca. 20
40 – 50	ca. 690	ca. 1180	20 – 22	n.d.	n.s.	n.d.	n.d.
50 - 60	ca. 480	ca. 40	30 – 32	n.d.	n.d.	-	-
60 - 70	n.d.	n.d.	38 – 40	-	-	n.d.	n.d.
80 - 90	n.d.	n.d.	40 – 42	n.d.	n.d.	-	-
100 - 110	n.d.	n.d.	48 - 50	-	-	n.d.	n.d.
119 - 129	n.d.	n.d.					

n.d. = not detected
- = not measured

At Apponaug Cove the phenolic benzotriazole profile indicates a much higher surface concentration than the lower sections of the core. Because the production of UV-328 was discontinued 12 years before the core was taken and the production of UV-327 25 years before that date, the authors attribute the high surface concentrations to resuspended sediment transport and deposition of materials in Apponaug Cove with relatively high

concentrations of phenolic benzotriazoles. The ratio of UV-327 to UV-328 also increases in the surface section and may indicate a disturbance of older sediments having higher UV-327 levels.

ANNEX 7: Available Information on Endocrine Disrupting properties of phenolic benzotriazoles

In-vitro-Studies
The estrogenic activity of several phenolic benzotriazoles was tested in a Yeast-Estrogen-Screen-assay (YES-assay) with human estrogenic receptors. In the study of Miller et al. (Miller et al., 2001) UV-327 and UV-329 (CAS 3147-75-9) were tested and in the study of Kawamura et al. (Kawamura et al., 2003) UV-327, UV-234 (CAS 70321-86-7), UV-326 (CAS 3896-11-5), UV-328 and UV-P (CAS 2440-22-4). Both studies showed that none of the phenolic benzotriazoles tested was triggering an estrogenic receptor activity.

In a study of Kunz et al. (Kunz et al., 2006) UV-360 (CAS 103597-45-1) was tested in a Yeast-Estrogen/Androgen-Screening-assay (YES/YAS-assay). No effects were reported.

In-vivo-Studies
In a recent review of the U.S. National Toxicology Program on the phenolic benzotriazoles UV-P, UV-329, UV-326, UV-320, UV-327, UV-328, UV-234, UV-360 as well as CAS 84268-36-0 (i.e. M1), 84268-33-7 (i.e. the methyl ester of M1), 84268-08-6 (i.e. a more complex ester of M1) and CAS 104810-48-2/104810-47-1 (i.e. an oligomeric ester of M1) (National Institute of Environmental Health Sciences, 2011) an overview over the available toxicity studies on mammals is given. There are several indications on effects mentioned that might be caused by endocrine disruption, e.g. reduced concentrations of testosterone, higher concentrations of CYP450, or higher activity of ethoxyresorufin-O-deethylase (EROD-activity). As in these cases there are also indications for toxic effects on the liver reported, the effects might actually be only secondary effects. With the present knowledge it is not possible to attribute them unambiguously as endocrine adverse effects.

Preliminary assessment of ED-properties for the phenolic benzotriazoles

There are several indications on effects of phenolic benzotriazoles mentioned that might be caused by endocrine disruption, e.g. reduced concentrations of testosterone, higher concentrations of CYP450, or higher activity of ethoxyresorufin-O-deethylase (EROD-activity). As in these cases there are also indications for toxic effects on the liver reported, the effects might actually be only secondary effects. With the present knowledge it is not possible to attribute them unambiguously as endocrine adverse effects of an equivalent level of concern.

Annex 8: RAC opinion

Committee for Risk Assessment

RAC

Opinion

on the specific target organ toxicity of

2-benzotriazol-2-yl-4,6-di-tert-butylphenol (UV-320)

EC number: 223-346-6

CAS number: 3846-71-7

and

2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328)

EC number: 247-384-8

CAS number: 25973-55-1

ECHA/RAC/A77-O-0000003444-77-02/F

Adopted

10 June 2013

10 June 2013
ECHA/RAC/ A77-O-0000003444-77-02/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT

ON THE SPECIFIC TARGET ORGAN TOXICITY OF

2-BENZOTRIAZOL-2-YL-4,6-DI-TERT-BUTYLPHENOL (UV-320) AND 2-(2H-BENZOTRIAZOL-2-YL)-4,6-DITERTPENTYLPHENOL (UV-328)

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on repeated dose toxicity of UV-320 and UV-328.

I PROCESS FOR ADOPTION OF THE OPINION

In the mandate of 4 April 2013 attached as Annex 1, the Executive Director of ECHA requested the RAC to provide an opinion on the specific target organ toxicity of UV-320 and UV-328 taking into account the information provided in Annex XV dossiers for the identification of substances of very high concern (SVHC) and the comments submitted on the 'T' hazard during the public consultation on these dossiers. It should be noted that this was not intended as a request for an opinion on harmonised classification and labelling as such; it was solely intended to provide advice to the Member State Committee (MSC) in this specific case.

The Annex XV SVHC dossiers were made publicly available at: http://echa.europa.eu/proposals-to-identify-substances-of-very-high-concern

on **4 March 2013**. Parties concerned and MSCAs were invited to submit comments and contributions by **18 April 2013**.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Boguslaw Baranski**

The RAC opinion was adopted on 10 June 2013.

The RAC opinion was adopted by consensus.

III OPINION OF THE RAC

The RAC has formulated its opinion on:

a) whether the information provided in the Annex XV SVHC dossiers is sufficient to develop an opinion of a similar robustness to a CLH opinion,

b) whether the information provided shows that the substance meets the criteria for classification for specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) under CLP.

After examination of the information provided in the SVHC Annex XV dossiers and the comments related to specific target organ toxicity following repeated exposure raised during the public consultation, the RAC agreed that this information shows that the substances UV-320 and UV-328 both meet the criteria for classification **as STOT RE 2** as defined in the CLP Regulation (EC) 1272/2008.

IV SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of specific target organ toxicity (CLP) – repeated exposure (STOT RE)

2-BENZOTRIAZOL-2-YL-4,6-DI-TERT-BUTYLPHENOL (UV-320)

Summary of the Dossier submitter's proposal

The dossier submitter (DS, German competent authority) proposed that UV-320 be classified for "specific target organ toxicity – repeat exposure" in sub-category 1 (STOT RE 1) and therefore be considered as toxic, complying with the 'T' criterion for PBT definition under the REACH Regulation. UV-320 is not registered under REACH.

The basis for the STOT RE 1 classification is derived from a sub-acute (28-day) toxicity study in rats (Hirata-Koizumi *et al*., 2007). Repeated oral (gavage) administration of UV-320 caused toxicity in several organs, in particular in the liver. Briefly, microscopic examination revealed hypertrophy of hepatocytes starting from 0.5 mg/kg bw/d. At higher dose levels (i.e. from 2.5 mg/kg bw/d), males showed hepatocellular vacuolar degeneration and focal necrosis. Bile duct proliferation was also observed from 0.5 mg/kg bw/d.

The DS concluded that because the LOAEL is < 10 mg/kg bw/d, the subcategory STOT RE 1 is fulfilled, in line with CLP classification criteria. In conclusion, based on the provisions of Annex XIII, section 1.1.3 (c) of the REACH Regulation, the DS also concluded that UV-320 meets the 'T' criterion.

Comments received during public consultation

Some comments provided support to the DS proposal on the identification of the substance as an SVHC. Other comments considered the available vPvB/PBT data relatively weak. One MS competent authority (CA) which did not specifically address STOT RE but emphasised the lack of robust information to conclude on the PBT/vPvB status.

Regarding STOT RE, a further MSCA requested additional details to properly assess the classification proposal. In particular, they asked for clarifications on whether the adverse toxicity effects reported were increased in a dose-related and statistically significant way. They also requested clarification from the DS regarding the choice of the key study and on the comparison with the CLP criteria.

The a third MSCA agreed with the DS on STOT RE 1 on the basis of severe toxicity occurring in several target organs (liver, heart, spleen) at a dose fulfilling the CLP criteria for STOT RE 1.

Assessment and comparison with the classification criteria

The RAC considers the information provided in the SVHC Annex XV dossier not to be sufficient to develop an opinion of a similar robustness to a CLH opinion, because the severity of the effects were not described in sufficient details and the effects were not analysed taking into account the guidance values (in mg/kg bw/day) provided in tables 3.9.2 and 3.9.3 of Annex I to the CLP regulation. In addition, the severity and significance of the effects were not compared with criteria provided in sections 3.9.2.7 and 3.9.2.8 of Annex I to the CLP Regulation. The references for two of the three studies considered in the SVHC Annex XV dossier were provided during public consultation.

Therefore, the results of studies considered by the DS (listed below and in the reference list) were summarized in this opinion and compared with classification criteria:

1. Hirata-Koizumi M, Watari N, Mukai D, Imai T, Hirose A, Kamata E, Ema M (2007). A 28-Day Repeated Dose Toxicity Study of Ultraviolet Absorber 2-(2´-Hydroxy -3´,5´-di-tertbutylphenyl) benzotriazole in Rats. Drug and Chemical Toxicology, 30: 327-341

2. Hirata-Koizumi M, Matsuyama T, Imai T, Hirose A, Kamata E, Ema M (2008a). Gonadal Influence on the Toxicity of 2- (2'- Hydroxy-3´,5´--di-*tert*-butylphenyl) benzotriazole in Rats. Drug and Chemicl Toxicology, 31: 115-126.

3. Hirata-Koizumi M, Ogata H, Imai T, Hirose A, Kamata E, Ema M (2008b). A 52-Week Repeated Dose Toxicity Study of Ultraviolet Absorber 2-(2'-hydroxy-3',5'-di*tert*butyl-phenyl) benzotriazole in Rats. Drug and Chemical Toxicology 31: 81-96.

CLP classification criteria for repeated target organ toxicity (STOT RE)

According to the CLP Regulation (section 3.9.2.) substances are classified as specific target organ toxicants following repeated exposure (STOT RE) by the use of expert judgement on the basis of the weight of all available evidence.

Substances are classified in Category STOT RE 1 on the basis of:

— reliable and good quality evidence from human cases or epidemiological studies; or

— observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations.

Substances are classified in Category STOT RE 2 on the basis of:

— observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. The classification is applicable when significant toxic effects are observed in a 90-day repeated dose study conducted in experimental animals at or below the guidance values provided in table 3.9.2 for Category 1 and table 3.9.3 of CLP Regulation for category 2. In case of oral exposure (rat) they are either ≤ 10 mg/kg/day for Category 1 or they are in a range between 10 and 100 mg/bw /day for Category 2

For a 28-day study this guidance value is increased by a factor of three.

As defined in section 3.9.2.7.3 of the CLP Regulation, all available evidence, and its relevance to human health, shall be taken into consideration in the classification process, including but not limited to the following toxic effects in humans and/or animals:

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites;

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);

(c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver);

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

It should be noted that as defined in point 3.9.2.8.1. of Annex I of CLP there are some effects in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity;

(b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptive responses that are not considered toxicologically relevant;

(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

Summary of target organ toxicity induced by UV-320 after repeated exposure

In the 28-day study of Hirata-Koizumi *et al.* (2007) females and male rats were administered UV-320 (2-benzotriazol-2-yl-4,6-di-tert-butylphenol) by gavage at a dose of 0 (vehicle: corn oil), 0.5, 2.5, 12.5, or 62.5 mg/kg bw/day for 28 days. This study was performed in compliance with the Test Guideline of the Japanese Chemical Control Act and in accordance with GLP. The initial numbers of rats were 10/sex in the control and the highest dose group, and 5/sex in other dose groups. The day after the last dosing, 5 males and 5 females from each group were euthanized for the assessment of hematology, blood biochemistry, organ weights, and macroscopic and microscopic findings.

The exposure to UV-320 did not result in treatment-related mortality or clinical signs of toxicity in any groups. There were also no significant changes in body weight, but a significant increase in food consumption was noted on dosing days 14 and 21 in males and on dosing days 21 and 27 in females at 62.5 mg/kg. No dose-related changes were found in the findings of urinalysis.

At the completion of dosing, a decrease in red blood cells, hemoglobin, and hematocrit was noted only in males at 2.5 mg/kg and more, but not in female rats. A small, although statistically significant reduction of red blood cells, hemoglobin, and hematocrit (amounting to 9%, 10.5% and 8.1% of the mean control values, respectively) was seen at the highest dose of 62.5 mg/kg bw/day. The degree of anemia at the highest dose does not meet the criteria of significant adverse effects (e.g. reduction in Hb at ≥ 20%) as defined in section 3.9.2.5.2 of the Guidance on the Application of the CLP Criteria for STOT RE classification.

Blood biochemical examination revealed statistically significant dose-dependent increases in:

- albumin level increased significantly from 3.78 g/dL in control males to 4.43 mg/dL and 4.40 mg/dL in rats exposed to 12.5 mg/kg and 62.5 mg/kg, no significant increase of albumin level was noted in females
- albumin/globulin ratio in males at 0.5 mg/kg and more (from 1.85 in controls to 3.05 in the 62.5 mg/kg group; in females increase in albumin/globulin ratio was noted only in the 62.5 mg/kg group; from 2.04 in controls to 4.21 in the 62.5 mg/kg group
- levels of glucose increased from 122 mg/dL in control males to 170, 170 and 156 mg/dL in male rats exposed to 2.5 mg/kg, 12.5 mg/kg and 62.5 mg/kg,

respectively and from 110 mg/dL in control females to 151 mg/dL in female rats exposed to 62.5 mg/kg,

- urea nitrogen (BUN) level increased significantly only in males exposed to 62.5 mg/kg –from 13.0 mg/L to 17.2 mg/L
- aspartate aminotransferase (AST) level increased significantly only in males exposed to 62.5 mg/kg –from 72 U/L to 115 U/L
- alanine aminotransferase (ALT) level increased significantly in male rats exposed to 62.5 mg/kg –from 30 U/L to 48 U/L and females – from 21 U/L to 33 U/L
- total cholesterol and triglyceride levels were increased only in females exposed at 62.5 mg/kg; cholesterol from 49 mg/dl in control females to 84 mg/dl in exposed females and triglyceride from 12.3 mg/dl in control females to 31.9 mg/dl in exposed females

From the changes described above, increased serum levels of AST, ALT, BUN, total cholesterol, triglyceride and glucose induced by UV-320 at the dose of 62.5 mg/kg are not by themselves considered sufficiently adverse effects. However, in conjunction with histopathological changes in the liver, they are considered as consistent and significant adverse effects which meet criterion of specific target organ toxicity-repeated exposure as set out in section 3.9.2.7.3 of CLP.

At necropsy, absolute liver weight was significantly increased in males from 9.4 g in control group to 17.1 g, 21.6 g and 24.5 g in males exposed to 2.5, 12.5 and 62.5 mg/kg respectively. In females there was a significant increase in absolute liver weight from 6.4 g in control group to 8.7 g and 12.4 g in females exposed to 12.5 and 62.5 mg/kg respectively. In the highest dose group (62.5 mg/kg), there was also a significant increase in absolute and relative kidney weight in males and in absolute heart weight in females. No test substance-related significant effects were detected in other organs.

During histochemical analysis test substance-related effects were observed in the liver, heart, kidneys, thyroids and spleen.

In the liver:

- hypertrophy of hepatocytes was observed in 3, 5, 5 and 5 out of 5 examined male rats exposed to 0.5, 2.5, 12.5 and 62.5 mg/kg, respectively and in 5 out of 5 examined female rats at 12.5 and 62.5 mg/kg; respectively
- hepatocellular fatty change was mostly observed in control animals: in males it was observed in 5 out of 5 control animals, while this change was not observed in exposed males; in females a hepatocellular fatty change was observed in 5 out of 5 examined control females and in females exposed to 0.5 mg/kg and 2.5 mg/kg, in 3 and in 0 females out 5 examined females exposed to 12.5 and 62.5 mg/kg; respectively
- vacuolar degeneration of hepatocytes was observed in 5 out of 5 examined male rats exposed to 2.5, 12.5 and 62.5 mg/kg, respectively and in 2 out of 5 examined female rats at 62.5 mg/kg
- increased mitosis of hepatocytes was observed in 4 out of 5 examined male rats exposed to 62.5 mg/kg, and in females in 1 and 2 out of 5 examined female rats exposed to 12.5 and 62.5 mg/kg; respectively
- focal necrosis was observed in 1, 2 and 4 out of 5 examined male rats exposed to 2.5, 12.5 and 62.5 mg/kg, respectively
- hepatocellular pigmentation and/or cytoplasmic inclusion bodies was observed in 1 out of 5 examined males exposed to 62.5 mg/kg
- bile duct proliferation was observed in 1, 1, 4 and 4 out of 5 examined male rats exposed to 0.5, 2.5, 12.5 and 62.5 mg/kg, respectively and in 1 out of 5 examined female rats at 62.5 mg/kg;

- the above histopathological changes were reported as slight for males and females. Except for increased mitosis, the effects were still present at the completion of the 14-day recovery period at the dose of 62.5 mg/kg.

In the heart:

- slight cell infiltration was observed in 5, 4 and 4 out of 5 examined male rats exposed to 2.5, 12.5 and 62.5 mg/kg, respectively and in 1 and 1 out of 5 examined female rats exposed to 0.5 and 62.5 mg/kg, respectively
- slight hypertrophy of the myocardium was observed in 3 and 4 out of 5 examined male rats exposed to 12.5 and 62.5 mg/kg, respectively and in 1 and 3 out of 5 examined female rats exposed to 12.5 mg/kg and 62.5 mg/kg, respectively
- slight degeneration of the myocardium was observed in 5 out of 5 examined male rats exposed to 12.5 and 62.5 mg/kg, and in 3 and 5 out of 5 examined female rats exposed to 12.5 mg/kg and 62.5 mg/kg, respectively
- except hypertrophy, the above histopathological changes were also reported in males only at the completion of the 14-day recovery period at the dose of 62.5 mg/kg.

In the kidneys:

- slight hypertrophy of the tubular epithelium was observed in the kidneys of 2 and 5 out of 5 examined male rats exposed to 12.5 and 62.5 mg/kg, respectively, and in 2 out of 5 examined females at 62.5 mg/kg
- slight to moderate basophilic tubules were observed in the kidneys of 2, 3, 4, 3, 5 out of 5 examined male rats exposed to 0, 0.5, 2.5, 12.5 and 62.5 mg/kg, respectively. The severity was moderate for 2 out of 5 male rats dosed at 62.5 mg/kg. Basophilic tubules were observed (with no clear dose-response or increased severity) in the kidneys of 1, 2, 2, 0, 3 out of 5 examined female rats exposed to 0, 0.5, 2.5, 12.5 and 62.5 mg/kg, respectively
- the above changes were completely recovered at the completion of the 14-day recovery period at the dose of 62.5 mg/kg.

In the thyroids:

- slight diffuse follicular cell hyperplasia was observed in 2 males and in 2 females out of 5 examined animals at 62.5 mg/kg
- diffuse hyperplasia was reported in 3 out of 5 males at the completion of the 14-day recovery period.

In the spleen:

- slight extramedullary hematopoiesis was observed in 3, 2 and 2 out of 5 examined male rats exposed to 2.5, 12.5 and 62.5 mg/kg, respectively and in 1 out of 5 examined female rats exposed to 0.5 mg/kg/day.
- after completion of the 14-day recovery period the slight extramedullary hematopoiesis was still seen in 3 out of 5 males at the dose of 62.5 mg/kg.

Hypertrophy of hepatocytes and increased mitosis of hepatocytes are considered as histopathological changes associated with the increased liver weight observed in this study. The liver hypertrophy is associated with an increase in absolute and relative weight of the liver in exposed animals. However, such changes do not meet the criterion of significant adverse effect as defined in section 3.9.2.7.3.e of CLP Regulation (multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity).

The focal necrosis incidence was found to be significantly increased in males, but not in female rats exposed to 62.5 mg/kg. The increased incidence of focal necrosis is in agreement with the dose-dependent and significantly increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and with changes in other

biochemical parameters occurring in rats exposed to 62.5 mg/kg. This is considered as sufficient evidence that UV-320 induced significant, adverse changes which meet the classification criteria for STOT RE.

In the 28-day study of Hirata-Koizumi *et al.* (2008a) castrated females and male rats were administered UV-320 (2-(2'-hydroxy-3',5'-di-tert-butylphenyl) benzotriazole) by gavage at doses of 0 (vehicle: corn oil), 0.5, 2.5 or 12.5 mg/kg bw/day for 28 days. The aim of this study was to explain the differences in sensitivity of male and female rats to the toxic properties of UV-320 as observed in a previous study of Hirata-Koizumi *et al.* (2007).

No deaths, clinical signs of toxicity, or changes in body weight or food consumption were found at any doses.

Blood biochemical examination revealed significant dose-dependent increases:

- albumin level increased significantly from 4.43 g/dL in control males to 5.03 mg/dL in male rats exposed to 12.5 mg/kg. A significant increase of albumin level (5.14 g/dL) was also noted in females exposed to 12.5 mg/kg in comparison to the controls (4.19 g/dL)
- levels of glucose increased from 176 mg/dL in control males to 199 and 196 mg/dL in male rats exposed to 0.5 mg/kg and 12.5 mg/kg, respectively, no increase in glucose level was noted in females rats,
- urea nitrogen (BUN) level increased significantly in males exposed to 12.5 mg/kg – from 15.8 mg/L to 19.7 mg/L, and in females from 20.0 mg/L to 23.2 mg/L .
- AST level increased significantly in males exposed to 12.5 mg/kg –from 61.1 U/L to 91.4 IU/L, and from 54.8 IU/L in control females to 62.4 IU/L in females exposed to 0.5 mg/kg, no increase in AST level was noted in females exposed to 2.5 and 12.5 mg/kg
- ALT level increased significantly in male rats exposed to 12.5 mg/kg –from 40.2 U/L to 55.5 U/L and no increase was noted in females exposed at any level
- ALP level increased significantly in male rats exposed to 12.5 mg/kg –from 868 IU/L to 1552.5 IU/L, and in female rats exposed to 12.5 mg/kg –from 727 IU/L to 1026 IU/L
- LDH level increased significantly in male rats exposed to 2.5 and 12.5 mg/kg –from 112 IU/L to 173 and 403 IU/L respectively , and in female rats exposed to 0.5, 2,5 and 12.5 mg/kg –from 138 IU/L to 254, 209 and 235 IU/L respectively
- creatinine level slightly decreased (to ca. 84% of the control value) in all exposed males, and females exposed to 2.5 and 12.5 mg/kg.

At necropsy, absolute liver weight was significantly increased in males from 15.5 g in the control group to 18.2 g, 21.6 g and 26.9 g in males exposed to 0.5, 2.5 and 12.5 mg/kg respectively. In females there was a significant increase in absolute liver weight from 14.5g in the control group to 27.0 g in females exposed to 12.5 mg/kg.

The histopathological examination was carried out on the organs of 10 animals per sex in each group and resulted in the following:

- very slight diffuse hypertrophy of hepatocytes was observed in 4, 10 and 10 out of 10 male rats examined which had been exposed to 0.5, 2.5 and 12.5 mg/kg/day, as well as in 2 and 9 out of 10 female rats exposed to 2.5 and 12.5 mg/kg/day. The cytoplasm of the hepatocytes was slightly eosinophilic.
- very slight to slight anisokaryosis was found in 1, 8 and 10 males exposed to 0.5, 2.5 and 12.5 mg/kg and in 5 and 8 females exposed to 2.5 and 12.5 mg/kg/day, which indicates disturbed production of erythrocytes.

- very slight to slight nucleolar enlargement in hepatocytes was found in 1, 10 and 10 males exposed to 0.5, 2.5 and 12.5 mg/kg and in 5 and 9 females exposed to 2.5 and 12.5 mg/kg/day
- very slight to slight decreased glycogen in hepatocytes was found in 1, 6 and 10 males exposed to 0.5, 2.5 and 12.5 mg/kg and in 2 and 8 females exposed to 2.5 and 12.5 mg/kg/day
- very slight increased mitosis of hepatocytes was found in 1 and 4 males exposed to 2.5 and 12.5 mg/kg and no change was seen in exposed females
- Very slight focal necrosis was observed in 3 out of 10 examined male rats exposed to 12.5 mg/kg, while in females, focal necrosis was observed in 3 and 2 out of 10 examined female rats exposed to 2.5 and 12.5 mg/kg

No substance-related histopathological findings were detected in the heart or the kidneys.

The nature of effects in the liver found in this study does not meet the criterion of significant adverse effect defined for specific target organ toxicity-repeated exposure and set out in section 3.9.2.7.3.c/e of CLP Regulation (consistent and significant adverse change in clinical biochemistry or multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity). Focal necrosis was noted only in 20 -30% of animals exposed to 2.5 and 12.5 mg/kg, and is consistent with liver cell damage in Hirata-Koizumi *et al*. 2007.

A 52-week repeated dose toxicity study with UV 320 was conducted according to OECD TG 452 under GLP (Hirata-Koizumi et al. 2008b). Twenty female and male rats per dose (CD(SD)IGS) were given UV 320 by gavage at 0, 0.1, 0.5, or 2.5 mg/kg/day (males) and 0, 0.5, 2.5, or 12.5 mg/kg/day (females). At the end of the 13-week administration period, 10 males and 10 females from each group were euthanized for the assessment of hematology, blood biochemistry, organ weights, and macroscopic and microscopic findings. The remaining animals in all groups (10 rats/sex/dose) were fully examined at the completion of the 52-week administration period.

No substance-related deaths or clinical signs of toxicity were observed in any group; however, a lowered body weight was found from day 36 to the end of the 52-week administration period at a dose of 2.5 mg/kg in males.

Where urine analysis is concerned, after 13-week exposure, a significant increase in osmotic pressure and specific gravity was detected at 2.5 mg/kg in males. No changes were noted in other parameters of urinalysis in any UV 320-treated groups (numerical data not provided). Urinalysis after 52-week exposure revealed a significant increase in osmotic pressure at 0.5 mg/kg (and above) in males, while it was significantly decreased at 12.5 mg/kg in females. A significant increase in urine volume was also detected at 12.5 mg/kg in females (numerical data not provided).

<u>Hematological examination after 13-week exposure</u>:

Males

- hemoglobin level – dose dependent decrease in males exposed to 0.5 and 2.5 mg/kg (up to 92% of the control value at the highest dose)
- hematocrit – dose dependent decrease in males exposed to 0.5 and 2.5 mg/kg (up to 92% of the control value at the highest dose of 2.5 mg/kg)
- Red blood cell count was decreased to 94.3% of the control value in males exposed to 2.5 mg/kg
- Platelet count was increased to 126.2% of the control value in males exposed to 2.5 mg/kg.

Females

- hematocrit significantly decreased to 95.3% of the control value and mean corpuscular volume (MCV) decreased to 96.9% of the control value noted only at 12.5 mg/kg.

On hematological examination after 52-week exposure:

Males:

- hemoglobin level not significantly affected by the treatment
- red blood cell count significantly decreased to 90% and to 92.6% of the control value in the at 0.5 mg/kg and 2.5 mg/kg respectively
- hematocrit decreased to 92,1 % of the control values at 2.5 mg/kg in males
- platelet count was increased to 131.5% of the control value in the 2.5 mg/kg male group
- prothrombin time (PT) was significantly prolonged to 161.5% of the control value in males exposed to 2.5 mg/kg.

Females:

- platelet count was increased to 117.1% of the control value in females exposed to 12.5 mg/kg.

The RAC noted that hematological changes induced by UV 320 were of slight intensity and the degree of anemia does not meet the criteria (reduction in Hb at ≥ 20%) defined in section 3.9.2.5.2 of the Guidance on the Application to CLP Criteria for STOT RE classification.

Blood biochemical examination after 13-week exposure:

Males:

- glucose serum level increased to 127% and 124% of the control value in males exposed to 0.5 and 2.5 mg/kg
- blood urea nitrogen increased in males exposed to 0.5 and 2.5 mg/kg (up to 123.3% of the control value at the highest dose), which indicates disturbance of kidney function
- alkaline phosphatase -ALP increased in males exposed to 0.5 and 2.5 mg/kg (up to 377.4% of the control value at the highest dose)
- increase in albumin/globulin ratio from 1.22 in controls to 1.67 and 2.09 in the 0.5 mg/kg and 2.5 mg/kg group respectively
- decrease in α_2- and β-globulin from 7.1% and 15.2 % in controls to 5.9 % and 11.5 % in the 0.5 mg/kg and to 5.6 % and 9.9 % in the 2.5 mg/kg group respectively

Females:

- total protein increase to 108% of the control value in a dose of 12.5 mg/kg in females
- albumin increase to 107.6% of the control value at the highest dose
- α2- and β-globulin decrease 5.6% and 12.6% in control females to 4.7% and 9.9% females exposed to 12.5 mg/kg control value in a dose of 12.5 mg/kg in females

There were no substance related changes in other blood biochemical parameters, including total bilirubin level.

Blood biochemical examination after 52 week exposure:

Males:

- alkaline phosphatase (ALP) significantly increased to 258% and to 400% of the control value in the 0.5 mg/kg and 2.5mg/kg group, respectively

- Blood urea nitrogen was increased to 140% of the control value only in males exposed to 2.5 mg/kg in males, which indicates disturbance of kidney function
- albumin, a dose dependent increase to 116.9% and to 127.2% of the control value in the 0.5 mg/kg and 2.5mg/kg group, respectively
- decrease in α_1-globulin to 79.2% and 69.8% of control value and in α_2-globulin to 81.3% and 66.7% of control value in the 0.5 mg/kg and 2.5mg/kg group
- decrease in β-globulin to 70.9% of the control value in 2.5 mg/kg male group
- albumin/globulin ratio was significantly increased to 140.5% and to 175% value in the 0.5 mg/kg and 2.5mg/kg male group, respectively.

Females:

- alkaline phosphatase (ALP) significantly increased to 150% of the control value in the 12.5 mg/kg female group
- Blood glucose level was increased to the 115.3% of the control value only in females at 12.5 mg/kg.

No substance-related changes were found in other blood biochemical parameters, including total bilirubin level (data not shown).

Conclusion on clinical chemistry findings

In the opinion of the RAC the nature and intensity of the changes in biochemical parameters were similar in animals exposed to UV-320 for 90 days (13 weeks) and in animals exposed for 52 weeks. The fact that the moderate intensity of changes in clinical biochemistry observed after 13-week exposure was not enhanced after an additional 39 weeks of exposure suggests that these changes alone observed after 90-day exposure do not meet the criterion defined in the CLP Regulation as consistent and significant adverse change in clinical biochemistry.

Pathological and histopathological examination after 13-week exposure

At necropsy after 13-week exposure, enlargement of the liver was observed in 5 out of 9 males at 2.5 mg/kg and in 1 out of 10 females at 12.5 mg/kg, and the absolute and relative liver weights were significantly increased at 0.5 mg/kg and higher in males, and at 12.5 mg/kg in females.

A significant increase in the relative weights of the brain, heart, kidneys, and testes were also found at 2.5 mg/kg in males after 13-week exposure, but the absolute weight was not significantly changed.

On histopathology, centrilobular hypertrophy of hepatocytes accompanied with eosinophilic granular cytoplasm was observed in the liver. The incidence of centrilobular hypertrophy of hepatocytes in males and females was significantly increased from 0 % in controls to 60% males in the 2.5 mg/kg group and from 0 % in controls to 60% of females at 12.5 mg/kg.

Focal necrosis was observed in 1 of control male, 1 male in the 0.5 mg/kg group and 2 out of 10 males in the 2.5 mg/kg group. In females focal necrosis was observed only in 1 out of 10 females in the 2.5 mg/kg group but in none of the females exposed to 12.5 mg/kg.

Pathological and histopathological examination after 52-week exposure

At necropsy after 52-week exposure, enlarged liver was observed in 7 out of 10 males at 0.5 mg/kg, 9 out of 10 males at 2.5 mg/kg, and 5 of 9 females at 12.5 mg/kg. Light gray macules were grossly detected in the liver of 2 out of 10 males at 2.5 mg/kg and of 1 out of 9 females at 12.5 mg/kg.

Absolute and relative liver weights were significantly increased at 0.5 mg/kg and higher in males, and at 12.5 mg/kg in females. A significant increase in the relative weights of the brain, pituitary, thyroids, lungs, heart, kidneys, testes and epididymides at 2.5 mg/kg in

males were also found, but no statistically significant change was noted in the absolute weight.

The increased incidence of centrilobular hypertrophy of hepatocytes accompanied with eosinophilic granular cytoplasm was observed in histopathological examination in none of the control animals, in 5 and 7 males out of 10 examined in the 0.5 mg/kg and 2.5mg/kg groups, respectively and in 4 females out of 9 examined in the 12.5 mg/kg group.

The lipofuscin deposition in hepatocytes, which indicate remnants of phagocytized cell debris was noted only in 6 out of 10 examined males exposed to 2.5 mg/kg, and in 2 out of 9 examined females exposed to 12.5 mg/kg.

The incidence of cystic degeneration of hepatocytes was noted in 2, 2 and 4 out of 10 examined males exposed to 0.1, 0.5 and 2.5 mg/kg, and in none of the control or exposed females.

The altered hepatocellular foci (clear cell foci) were found in the liver of 1, 7 and 6 rats out of 10 examined males exposed to 0.1, 0.5 and 2.5 mg/kg, respectively, and in none of the control or exposed females.

The incidence of focal necrosis was not statistically increased in any exposed group and focal necrosis was seen in 3 and 4 out of 10 examined male rats exposed to 0.5 and 2.5 mg/kg, respectively, and in 2 control female rats while it was not seen in exposed females.

Comparison of effects with classification criteria

It is concluded by the RAC that the most frequent histopathological change in animals exposed for 13 weeks to UV 320 was a centrilobular hypertrophy of hepatocytes having eosinophilic granular cytoplasm in the liver, which is not relevant for classification. The incidence of focal necrosis in the liver was not statistically increased in any experimental group after 13-week or 52-week exposure and this change was not considered also by the authors of the study as treatment related. There were indications on liver cell degeneration from 28-day, 13-week and 52-week studies at doses of 2.5 mg/kg and above. However, 100% incidence of this histopathological change in the 28-day study, was not observed in the 52-week study, where only 4 of 10 males showed cystic degeneration and lipofuscin deposition was found in the liver of 6 out of 10 males. Taking into account that a dose of 2.5 mg/kg is below the guidance value of 30 mg/kg for category STOT RE 1 (for 28 day study), these findings were not considered sufficiently robust to justify category 1 due to lack of detailed information on the severity of these lesions.

Degenerative/necrotic liver changes which are in compliance with the observed increased activity of AST occurred in all animals at exposure level of 62.5 mg/kg, which is above the guidance value for classification as STOT RE 1 (30 mg/kg/day for 28-day studies), but within the guidance values for classification to category STOT RE 2 (30 mg/kg $< C \leq$ 300 mg/kg).This high dose was not tested in 13-week and 52-week studies. The myocardial degeneration observed at 12.5mg/kg and above in 28-day study was considered as adverse health effect and support the proposed classification.

In conclusion, the RAC is of the opinion that the information provided shows that the substance UV-320 meets the criteria for classification in **STOT RE 2** with hazard statement **H373** "May cause damage to liver through prolonged or repeated exposure". The organ affected after repeated administration of UV-320 is the **liver**.

2-(2H-BENZOTRIAZOL-2-YL)-4,6-DITERTPENTYLPHENOL (UV-328)

Summary of the Dossier submitter's proposal

The dossier submitter (DS, German competent authority) proposed that UV-328 be classified as "specific target organ toxicity – repeat exposure" in sub-category 2 (STOT RE 2) and therefore be considered as toxic, complying with the 'T' criterion for PBT definition under the REACH Regulation. UV-328 is registered under REACH (REACH registration dossier for UV-328, 2013). The REACH dossier is available on the ECHA dissemination database[22] and has been taken into account for this opinion.

The basis for the STOT RE 2 classification is derived from a sub-acute (49-day)/sub-chronic (90-day) repeated dose toxicity study conducted in rats (TNO, 1968, reported by EPA[23]). Repeated oral (gavage) administration of UV-328 caused toxicity in several organs, in particular in the liver. Briefly, microscopic examination revealed occasional foci of necrosis and a slight proliferation of bile duct epithelia. Parenchymal cells were enlarged. In the kidney, tubular necrosis was observed in some males from the higher feeding levels.

The DS did not present detailed information, concluding that the liver, bile duct and kidney effects meet the classification criteria for STOT RE 2. In addition, the majority of registrants self-classify UV-328 as STOT RE 2. In conclusion, based on the provisions of Annex XIII, section 1.1.3 (c) of the REACH Regulation, the DS also concluded that UV-328 meets the 'T' criterion.

Comments received during public consultation

Some comments provided support to the DS proposal on the identification of the substance as a SVHC. One MSCA which did not specifically address "specific target organ toxicity – repeat exposure" (STOT RE), emphasised the lack of robust information to conclude on the vPvB/PBT status. On the hazard profile of the phenolic benzotriazoles in general, a stakeholder (STO) mentioned that the specific substitution pattern on the phenolic group influences their toxicity. As a consequence, a general read-across may not be appropriate for all endpoints.

Regarding STOT RE, another MSCA requested additional details to properly assess the classification proposal. In particular, they requested clarifications on whether the adverse toxicity effects reported were increased in a dose-related and statistically significant way (in particular for kidney tubular necrosis and focal or multifocal necrosis in the liver).

One STO commented on the weakness of the 'T' criterion (STOT RE 2, based on a NOAEL of 100 ppm, i.e. 22 mg/kg bw/d) although it concluded that the substance formally meets the criteria for 'T'. Another STO agreed with the DS proposal, referring to the Lead Registrant that has also concluded positively on the 'T' criterion.

A third MSCA supported the DS's proposal on STOT RE 2 on the basis of toxicity occurring in several target organs (liver, bile duct , kidney, blood) with a NOAEL set at 100 ppm (22 mg/kg/d).

Assessment and comparison with the classification criteria

In the opinion of the RAC the information provided in the SVHC Annex XV dossier is not sufficient to develop an opinion of a similar robustness to a CLH opinion, because the severity of the effects was not described in sufficient details and the effects were not analysed taking into account the guidance values (in mg/kg bw/day) provided in tables 3.9.2 and 3.9.3 of Annex I to the CLP Regulation. The severity of the effects was also not compared with criteria of severity and significance of effects provided in sections 3.9.2.7 - 3.9.2.8 of Annex I to the CLP Regulation. The information on exposure was limited to a feeding level expressed in ppm as content of UV-328 in animal feed.

Therefore the original study report of Til *et al.* (1968) entitled 'Short-term (49-day) and sub-chronic (90-day) toxicity studies with "RY 1137" in rats' was used to prepare a robust

[22] http://echa.europa.eu/information-on-chemicals/registered-substances
[23] http://ofmpub.epa.gov/oppthpv/quicksearch.display?pChem=100705

study summary in order to enable the independent assessment of the results and their comparison with the classification criteria.

In addition, the original study report of Geigy (1970) entitled 'Three months Toxicity Study. Tinuvin 328. Dietary administration – Beagle Dogs' was summarized in this opinion.

The results of all studies were compared with CLP classification criteria for repeated target organ toxicity (STOT RE) provided in section on UV-320.

Summary of target organ toxicity induced by UV-328 after repeated exposure

The DS proposed to classify UV-328 for repeated toxicity using the results of the 90-day study on rats (Til *et al.* (1968)) which are summarised below.

2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (UV-328) was given to female and male rats in the feed at concentration of 100, 200, 400, 800 and 1600 ppm for 90 days (Til *et al.* 1968). The dose levels for males during the first and last two weeks of study amounted approximately to (respectively): 0 mg/kg bw/day, 13.2 - 5.8 mg/kg bw/day, 22.2 – 11.5 mg/kg bw/day, 48.7 – 25.6 mg/kg bw/day, 98.7 – 52.7 mg/kg bw/day and 190.9 – 120.5 mg/kg bw/day. For female rats in the same periods of study the dose levels were: 0 mg/kg bw/day, 13.1 – 6.8 mg/kg bw/day, 24.6 – 13.1 mg/kg bw/ day, 46.9 – 26.7 mg/kg bw/day, 91.7 – 56.0 mg/kg bw/day and 189.8 – 118.0 mg/kg bw/day.

No treatment-related deaths occurred at any feeding level. Decreased body weight occurred in the highest feeding levels: 190.9 – 120.5 mg/kg bw/day in males and 189.8 – 118.0 mg/kg bw/day in females.

Hematological examinations at week 12 revealed a dose dependent decrease of hemoglobin content in blood starting in males from a feeding level of 22.2 – 11.5 mg/kg bw/ day and in females from a dose level of 91.7 – 56.0 mg/kg bw/day. The extent of reduction of hemoglobin in males exposed to the highest feeding level amounted to 12% of the control group value, while in females exposed to the highest feeding level amounted to 6 % of the hemoglobin level in the control group. The extent of reduction in the percentage of packed cell volume (haematocrit or erythrocyte volume fraction) was proportional to the reduction of hemoglobin content.

Glucose 6-phosphatase activity in pooled livers and kidneys of 5 males and 5 females per group was increased at all levels including the lowest level (100 ppm). The increase of specific glucose 6-phosphatase activity was not dose- dependent. No other biochemical examinations were done.

The relative weights (expressed in g per 100 g of body weight) of the liver, kidneys and thyroid were increased. Average relative liver weights were distinctly increased at all feeding levels in both sexes. The extent of the liver enlargement after 3 months was much less than that observed in rats of the same dose group after 4 weeks. Relative kidney weights were increased at the three highest dose levels in males as well as in females. Relative thyroid weights were higher than those of the controls in both sexes starting from the dose level of 200 ppm. Relative spleen weights of male rats were increased at the 800 and 1600 ppm level, and relative testis weights were increased at the three highest dose levels.

Pathological examinations

Liver

Gross pathologic examination after 13 weeks revealed distinct enlargement and greenish-drab discoloration of livers. In males, discoloration was observed at all dose levels, in females only at 800 and 1600 ppm (91.7 – 56.0 mg/kg bw/day and 189.8 – 118.0 mg/kg bw/day, respectively).

Microscopic examination of the livers revealed hepatic damage at all dose levels in males and females, which decreased in severity with decreasing dietary levels of the test substance. Foci of necrosis were occasionally present in males, and in smaller number in females, at the 800 and 1600 ppm feeding levels – respectively in males at dose levels of

98.7 – 52.7 mg/kg bw/day and 190.9 – 120.5 mg/kg bw/day, and in females of 91.7 – 56.0 mg/kg bw/day and 189.8 – 118.0 mg/kg bw/day.

At these feeding levels, extremely enlarged parenchymal cells with very homogeneous, strongly eosinophilic cytoplasm, often containing yellowish-green, non-birefringent pigment granules and also big eosinophilic, hyaline droplets were found, in males more frequently than in females. The nuclei were often considerably enlarged, showed varying amounts of chromatin and many big nucleoli. There were an increased number of binucleated hepatocytes, a few pyknotic nuclei and necrotic cells. There was also slight proliferation of bile ducts.

The hepatic damage described above occurred to a lesser extent also at the 400, 200 and 100 ppm level. Foci of necrosis no longer present in males at these lower dose levels were visible incidentally in females. Parenchymal cells were distinctly enlarged also at the lowest feeding level, with nuclei varying in size, shape and quantity of chromatin. Yellowish-green pigment and eosinophilic droplets occurred only in males; an increased number of binucleated hepatocytes and a few necrotic hepatocytes were visible in both sexes. Slight proliferation of bile duct epithelium was found in some instances.

Kidneys

Greenish discoloration of kidneys occurred in males and females at the two highest feeding levels (800 and 1600 ppm).

Microscopic examination of kidneys revealed tubular nephrosis at the two highest feeding levels in males – respectively: 98.7 – 52.7 mg/kg bw/day and 190.9 – 120.5 mg/kg bw/day. This renal injury consisted of tubules with narrowed lumens and thickened basement membranes lined by epithelium with little and scarcely staining cytoplasm and big vesicular nuclei.

In females yellowish-brown pigment granules in the cytoplasm of proximal tubular cells were noticed at 200 ppm (24.6 – 13.1 mg/kg bw/ day) and above; the amount of the pigment increased with increasing levels of UV-328.

The RAC noted that the histopatological changes observed in the liver and kidneys in males rats exposed to 98.7 – 52.7 mg/kg bw/day meet the criteria of severe, adverse health effects defined for classification as STOT RE set in section 3.9.2.7.3. of Annex I to the CLP Regulation:

"(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver);"

In the study reported by Geigy (1970) beagle dogs received the test material 2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol (TINUVIN 328) for 3 months in their diet. The test material concentration in the diet was chosen and adapted in such a way that the following daily doses resulted in the five groups treated with test material: 15, 30, 60, 120 and 240 mg/kg body weight. Each treated group consisted of 3 male and 3 female beagle dogs. In addition 5 male and 5 female beagle dogs served as control.

One male dog in the highest dose group died during the 8th week of test material administration. Depression of the food consumption and loss of body weight were observed in the higher dose groups. The dogs in which these symptoms were most pronounced showed a sleepy and weak behavior. The ophthalmic examinations did not reveal noteworthy findings.

Hematology

The test material produced a considerable number of toxic symptoms which were in general more pronounced in the male dogs than in the female dogs. It seems that some toxic effects in the male dogs were as strong as or even stronger in the 120 mg/kg-group than in the 240 mg/kg-group.

Changes in the erythrocytes and hemoglobin which consisted of a decrease in number of erythrocytes, diminution of packed cell volume, decrease in hemoglobin content of blood, increase of mean corpuscular volume and decrease of mean corpuscular hemoglobin concentration were seen in dogs treated with 120 mg/kg and 240 mg/kg.

The mean red blood cell counts in male control dogs and in male dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months amounted, respectively to 6.76 x 10^6, 6.85 x 10^6, 6.85 x 10^6, 6.39 x 10^6, 4.55 x 10^6 and 6.99 x 10^6 /µl.

The mean red blood cell counts in female control dogs and in female dogs exposed to 15, 30 , 60 120 and 240 mg/kg bw/day for 3 months amounted, respectively to 7.13 x 10^6, 7.47 x 10^6, 7.27 x 10^6, 7.29 x 10^6, 6.84 x 10^6 and 5.98 x 10^6/µl.

The mean hemoglobin concentration in male control dogs and in male dogs exposed to 15, 30, 60 120 and 240 mg/kg bw/day for 3 months amounted, respectively to 15.7, 16.1,15,8, 15.5, 10.5 and 16.3 g/100ml.

The mean hemoglobin concentration in female control dogs and in female dogs exposed to 15, 30, 60 120 and 240 mg/kg bw/day for 3 months amounted, respectively to 16.2, 17.5, 17.2, 16.8, 16.2 and 13.1 g/100ml.

It is noted that reduction in level of hemoglobin in males at dose of 120 mg/kg, but not at dose of 240 mg/kg, and in females only in dose of 240 mg/kg were of ≥ 20% of hemoglobin level in the control animals thus meeting criteria of reduction in hemoglobin concentration as defined in section 3.9.2.5.2 of the Guidance in the Application to CLP Criteria for STOT RE classification. However, this effect does not warrant UV-328 to be classified as hematotoxic substance to STOT RE 2 category because the effect was observed only at doses above a guidance value of 100 mg/kg, and it was also not dose-dependent in males.

Clinical biochemistry

The glucose concentration in blood was affected by exposure in female and male dogs except for dog 240-5e exposed to 240/mg/kg, which died after 8 weeks of exposure.

The activity of GPT (glutamate pyruvate transaminase or alanine transaminase (ALT), GOT (glutamic-oxaloacetic transaminase or aspartate transaminase (AST) and alkaline phosphatase (ALP) in serum was increased. These enzyme activities mostly increased with the time of test material administration and/or included lower dose groups during the test material administration.

In the male dogs increased activities of these three enzymes were already seen in the 15 mg/kg-group; in the female dogs high activities of the serum ALP were found in the 15 mg/kg-group:

- alanine aminotransferase (ALT or GPT) level increased from a value of 7.8 mU/ml in control male dogs to values 70.9, 52.3, 119.9, 98.9 and 85.4 mU/ml, respectively in male dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months
- alanine aminotransferase (ALT or GPT) level increased from a value of 10.6 mU/ml in control female dogs to values 13.1, 48.5, 28.9, 59.7 and 96.1 mU/ml, respectively in female dogs exposed to 15, 30, 60 120 and 240 mg/kg bw/day for 3 months
- aspartate aminotransferase (AST or GPT) level increased from a value of 13.4 mU/ml in control male dogs to values 41.1, 22.4, 42.9, 56.7 and 30.8 mU/ml, respectively in male dogs exposed to 15, 30 , 60 120 and 240 mg/kg bw/day for 3 months

- aspartate aminotransferase (AST or GPT) level changed from a value of 16.8 mU/ml in control female dogs to values 13.1, 21.5, 19.6, 27.5 and 66.7 mU/ml, respectively in female dogs exposed to 15, 30, 60 120 and 240 mg/kg bw/day for 3 months
- alkaline phosphatase (ALP) level changed from a value of 22 mU/ml in control male dogs to values 96, 253, 236, 290 and 245 mU/ml, respectively in male dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months
- alkaline phosphatase (ALP) level changed from a value of 39 mU/ml in control female dogs to values 84, 206, 373, 207 and 498 mU/ml, respectively in female dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months.

Total protein in serum was diminished in exposed male and female dogs with the lowest value in dogs exposed to 240 mg/kg bw/day for 3 months being 86% of the control group value in exposed males and 81.5% of the control group value in exposed females.

Changes in the protein pattern (electrophoresis) in serum were observed in the 30 mg/kg-group and in higher dose groups. Prothrombin time, blood clotting time, urea-nitrogen as well as sodium and potassium concentrations in serum were normal.

An increased bilirubin concentration was determined in male dogs of all dose groups; dog 240-5e showed an extremely high figure.

- total bilirubin level in serum increased from a value of 2.5 mg/l in control male dogs to values 7.7, 5.4, 5.4, 6.0 and 2.85 mg/l, respectively in male dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months; bilirubin level determined just before death in dog which died after 8 weeks of exposure was above 180 mg/kg.
- total bilirubin level in serum female dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months was not affected by the treatment.

Pathological examinations

At necropsy after 3 months of exposure 1 out of 3 male dogs exposed to 120 mg/kg and 1 male dog exposed to 240 mg/kg, which died after 8 weeks of exposure, had icterus universalis (jaundice). One out of 3 female dogs exposed to 240 mg/kg showed a slighter degree of icterus.

At necropsy, absolute liver weight was significantly increased in male dogs from 399g in control group to 583g, 494g, 565g, 408g and 436g in male dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months, respectively. In females there was a significant increase in absolute liver weight from 303g in control group to 363g, 470g, 464g, 525g and 353g in female dogs exposed to 15, 30, 60, 120 and 240 mg/kg bw/day for 3 months, respectively.

The liver is severely affected by administration of UV-328. Several of the changes appeared already in the 15 mg/kg-group, e.g. fatty changes in Kupffer cells (specialized macrophages located in the liver lining the walls of the sinusoids), protein globules in cytoplasm, yellow pigmentation in Kupffer cells and Kupffer' cell hyperplasia; fatty degeneration of hepatocytes was only seen in dogs of 60 mg/kg-group and in higher dose groups.

The flowing changes were observed in the liver of male and female dogs:

- Kupffer cell hyperplasia: in 1 control female, in all 3 females exposed to 15 mg/kg, in one female and 1 male dog exposed to 30 mg/kg, in 2 males and 3 females exposed to 60 mg/kg; in 2 males and 2 females exposed to 120 mg/kg; in 3 males and 2 females exposed to 240 mg/kg;
- Fatty changes in Kupffer cells: in 1 male at 15mg/kg, 3 males at 30 mg/kg, and 1 female at 120 mg/kg
- Fatty degeneration of hepatocytes:
    - monocellular fatty changes: in 3 males at 60 mg/kg, 3 females at 240 mg/kg

  - o focal fatty degeneration, partly central and partly peripheral: in 2 females at 60 mg/kg, 2 males at 120 mg/kg, and 2 males at 240 mg/kg
  - o diffuse fatty degeneration: in 1 male dog at 240 mg/kg
- Centrolobular cholestasis: in 1 male at 60 mg/kg, 120 mg/kg and 240 mg/kg
- Monocellular necrosis: in 1 male and in 1 female at 30 mg/kg and in 1 female at 240 mg/kg
- Fibrosis: in 1 male at 60 mg/kg
- Inflammation: in 1 male at 60 mg/kg and 1 male at 240 mg/kg.

According to the study, the findings did not indicate a clear relationship between dose and the strength of the changes of the liver.

Comparison of effects with classification criteria

Focal necrosis of the liver and tubular nephrosis caused by UV-328 in male and females rats (Til *et al.*, 1968) at the feeding level of 800 ppm (respectively in males at dose levels of 98.7 – 52.7 mg/kg bw/day, and in females of 91.7 – 56.0 mg/kg bw/day), meet the criteria of significant toxic effects, of relevance to human health, produced at exposure concentrations meeting guidance values for category STOT RE 2 (10 < C ≤100 mg/bw /day).

The pathological changes in the liver and kidneys observed at lower dose levels of 100 ppm (ca. 10mg/kg/day), 200 ppm (ca. 15 mg/kg/day) and 400 ppm (ca. 30 mg/kg bw/day) do not meet the criteria of severity and toxicological significance defined in CLP criteria such as multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity or severe morphological changes that are potentially reversible but provide clear evidence for marked organ dysfunction (e.g. severe fatty change in the liver).

Small changes in clinical biochemistry such as increased glucose 6-phosphatase activity in pooled livers and kidneys observed at the dose level of 100 ppm corresponding to ca. 10mg/kg bw/day or in hematology such as small reduction (less than 5% in hemoglobin concentration and in packed cell volumes) observed in males, but not in females at the dose level of 200 ppm corresponding to ca. 15 mg/kg bw/day are of minimal toxicological importance and does not warrant classification.

The histopatological effects observed in dogs exposed to 60 mg/kg such as fatty degeneration of hepatocytes and fibrosis meet the criteria of classification in STOT RE hazard class defined in section in 3.9.2.7.3.(d)–(g) of CLP Regulation.

The considerable changes in the activity of several enzymes in serum and changes observed in protein pattern in serum in animals exposed to 15 mg/kg or higher support classification as STOT RE. Taking into account that these effects were observed in exposure levels ranging from 10 to 100mg/kg bw/day, UV-328 should be classified in category 2 of specific target organ toxicity – repeated exposure.

In conclusion, the RAC is of the opinion that the information provided shows that the substance UV-328 meets the criteria for classification in **STOT RE 2** with the hazard statement **H373** "May cause damage to organs (**liver, kidneys**) through prolonged or repeated exposure".

Supplemental information

Individual histopatological changes in reproductive organs of female and male dogs treated with UV-328 for 90 days (Geigy, 1970) are reported in the table below for information. Indeed, according to CLP Annex I, section 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class.

Table: Individual histopatological changes in reproductive organs of female and male dogs treated with UV-328 for 90 days (Geigy, 1970).

Dose in mg/kg bw/day	**0 (control)**	**15**	**30**	**60**	**120**	**240**
Testis						
	Dog C-3 Tubules with only Sertoli cells		**Dog 30-3***: several giant spermatogonia and multinucleated giant cells in tubules	**Dog 60-3**: several multinucleated giant cells in tubules and a slight chronic inflammation in the capsule **Dog 60-5**: strong defect in spermiogenesis, a distinct atrophy of the tubules, hyperchromia and hyperplasia of the spermatogonia and multinucleated giant cells.	**Dog 120-1**: moderate atrophy **Dog 120-3**: disturbances of spermiogenesis and progressing atrophy **Dog 120-5**: disturbances of spermiogenesis, round cell infiltration of interstitial tissue with hyperplasia of Leydig' cells and nearly no spermatocytes in the lumina of tubules	**Dog 240-3**: disturbances of spermiogenesis, slight atrophy of tubular epithelium and multinucleated giant cells **Dog 240-5e****: disturbances of spermiogenesis, slight atrophy of tubular epithelium and multinucleated giant cells
Prostate						
			Dog 30-5: slight atrophy of the glands and a slight increase of stroma	**Dog 60-1**: glandular epithelium is slightly flattened **Dog 60-5**: atrophy of the glands and a increase of stroma	**Dog 120-3**: slight atrophy of the glands **Dog 120-5**: very strong atrophy and sclerosis of the stroma.	**Dog 240-3**: very strong atrophy and sclerosis of the stroma **Dog 240-5e****: very strong atrophy and sclerosis of the stroma
Uterus						
				Dog 60-2: slight atrophy of all layers of the uterus wall	**Dog 120-4**: slight atrophy of all layers of the uterus wall	**Dog 240-6**: slight atrophy of all layers of the uterus wall **Dog 240-4**: atrophy of all layers of the uterus wall

*First number is a dose level in mg/kg followed by a number of male (1,3 and 5) or female (2,4 and 60) dog in this study; ** dog 240-5e died after 8 weeks of treatment; dogs were mature at study start (male dogs: 35 weeks; female dogs 32 weeks)

No histopatological examinations of male and female reproductive organs of rats were done in the 90-day study of Til *et al.* (1968) study, but in male rats exposed to dose levels of 48.7 – 25.6 mg/kg bw/day, 98.7 – 52.7 mg/kg bw/day and 190.9 – 120.5 mg/kg bw/day the relative weight of testis was significantly increased.

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ANNEXES

Annex 1	Request from the Executive Director of ECHA to the RAC of 4 April 2013 I(2013)0093 – 'the mandate'.
Annex 2	Annex XV dossier – Proposal for identification of a substance as a CMR 1A or 1B, PBT, vPvB or a substance of an equivalent level of concern (UV-320)
Annex 3	Annex XV dossier – Proposal for identification of a substance as a CMR 1A or 1B, PBT, vPvB or a substance of an equivalent level of concern (UV-328)

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ANNEX 9: Abbreviations

°C	Degrees centigrade
Å	Angstrom
avg.	Average
B	Bioaccumulative
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BOD_x	Biological oxygen demand in x days
BMF	Biomagnification factor
CAS	Chemical Abstracts Service
CLP	Classification, labelling and packaging (of substances and mixtures)
C&L	Classification and labelling
cm	Centimetres
cm²	Centimetres squared
cm³	Cubed centimetres
CMR	Carcinogenic, mutagenic, toxic to reproduction
CYP450	Cytrochrome P 450
d	Day
DDT	Dichlorodiphenyltrichloroethane
DegT50	Time interval after which 50% of a substance is degraded
DF	Detection frequency
DT_{50}	Time interval after which 50% of a substance is degraded or disappeared otherwise from the test medium
DisT50	Time interval after which 50% of a substance disappeared from the test medium (no degradation)
dw	Dry weight
EC	European Community
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EROD	Ethoxyresorufin-O-deethylase
EU	European Union
g	grammes
GC	Gas chromatography
GC/MS	Gas chromatography – mass spectrometry
GC-MS/MS	Gas chromatography – tandem mass spectrometry
GC-HRMS/LRMS	Gas chromatography – high resolution mass spectrometry/low resolution mass spectrometry
GLP	Good laboratory practice
h	Hour
H 351	Classification: suspected of causing cancer
H 373	Classification: May cause damage to organs through prolonged or repeated exposure
H 412	Classification: Harmful to aquatic life with long lasting effects
HALS	Hindered Amine Light Stabilizers
HHCB	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-[g]-2-benzo-pyrane, a polycyclic musk, CAS 1222-05-5
HPLC	High performance liquid chromatography
HPLC-MS/MS	High performance liquid chromatography – tandem mass spectrometry
IUPAC	International Union of Pure and Applied Chemistry
k	Rate constant (e.g. for biodegradation in sewage treatment plants)
$K_{air\text{-}water}$	Air-water partition coefficient
Kg	Kilograms
Km	Kilometres

Koc	Organic carbon-water partition coefficient
Kow	Octanol/water partition coefficient (log value)
Kp	Partition coefficient
KPa	Kilopascals
L (or l)	Litres
LC	Liquid chromatography
LC-MS	Liquid chromatography – mass spectrometry
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LC50	Lethal concentration for 50% of the test organisms
LOD	Limit of detection
LOQ	Limit of quantification
lw	Lipid weight
M	Molar
m^2	Metres squared (area)
m^3	Cubed metres (volume)
Max	Maximum
Min	Minimum
MITI	Ministry of International Trade and Industry (Japan)
mg	Milligrams
ml	Millilitres
ML	Megalitre
Mol	Moles
Mmol	Millimoles
MS	Mass spectrometry
µg	Micrograms
n	Number (e.g. number of samples)
n.d.	Not detected
NER	Non-extractable residues
NITE	National Institute of Technology and Evaluation, Japan
nm	Nanometres
NOEC	No-observed effect concentration
oc	Organic carbon
OECD	Organisation for Economic Co-operation and Development
P	Persistent
Pa	Pascals
PBDE	Polybromodiphenyl ether
PBT	Persistent, bioaccumulative and toxic
PCB	Polychlorinated biphenyl
POP	Persistent organic pollutant
PPB	Parts per billion
PPM	Parts per million
QSAR	Quantitative structure-activity relationship
QPREF	QSAR Prediction Reference Format
QSPR	Quantitative structure-property-relationship
r^2	Correlation coefficient
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals Regulation (EC 1907/2006)
Rel.	Reliability according to the Klimisch Score
s	Seconds (time)
SIM	Selective ion monitoring
SPIN	Database of substances in products in the Nordic countries
std.dev.	Standard deviation
STOT-RE	Specific target organ toxicity – repeated exposure
SVHC	Substances of very high concern
Σ	Sum
T	Toxic (hazard classification)
US or USA	United States of America

UV	Ultraviolet
UV-234	A phenolic benzotriazole UV stabilizer, CAS 70321-86-7
UV-320	2-benzotriazol-2-yl-4,6-di-tert-butylphenol, CAS 3846-71-7
UV-326	A phenolic benzotriazole UV stabilizer, CAS 3896-11-5
UV-327	2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol, CAS 3864-99-1
UV-328	2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol, CAS 25973-55-1
UV-329	A phenolic benzotriazole UV stabilizer, CAS 3147-75-9
UV-350	2-(2H-benzotriazol-2-yl)-4-(tert-butyl)-6-(sec-butyl)phenol, CAS 36437-37-3
UV-360	A phenolic benzotriazole UV stabilizer, CAS 103597-45-1
UV-571	A phenolic benzotriazole UV stabilizer, CAS 125304-04-3
UV-928	A phenolic benzotriazole UV stabilizer, CAS 73936-91-1
UV-P	A phenolic benzotriazole UV stabilizer, CAS 2440-22-4
vB	Very bioaccumulative
vP	Very persistent
vPvB	Very persistent, very bioaccumulative
w.a.	When applicable
ww	Wet weight
WWTP	Waste water treatment plant
YES	Yeast-estrogen-screen
YES/YAS	Yeast-Estrogen/Androgen-Screening