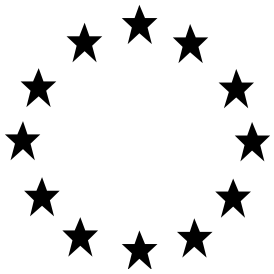
Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Cybutryne
Product type PT 21
(Antifouling)

May 2014

Netherlands

CONTENTS

1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 Procedure followed

This assessment report has been established as a result of the evaluation of the active substance cybutryne as product-type 21 (antifouling products), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Cybutryne (Cas no. 28159-89-0) was notified as an existing active substance, by Ciba Specialty Chemicals Inc. (which was taken over during the evaluation by BASF in 2009), hereafter referred to as the applicant, in product-type 21.

Commission Regulation (EC) No 1062/2014 of 4 August 2014 lays down the detailed rules for the evaluation of the dossiers and for the decision-making process.

On 30 April 2006 the Dutch competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 11 September 2006.

On 7 April 2011 the Rapporteur Member State submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Commission organised consultations via the Technical Meetings and the Agency organised consultations via the BPC and its Working Groups. Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

1.2 Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of cybutryne for product-type 21, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and the conclusions of this assessment report, which is available from the Agency web site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

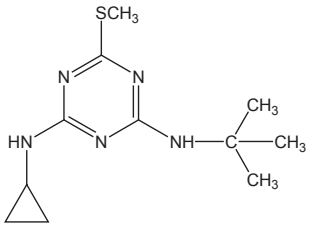
2 OVERALL SUMMARY AND CONCLUSIONS

2.1 Presentation of the Active Substance

2.1.1 Identity, Physico-Chemical Properties & Methods of Analysis

Identity

ISO common name	Cubytryne (published)
Chemical name (IUPAC)	N^2-tert-butyl-N^4-cyclopropyl-6-methylthio-1,3,5-triazine-2,4-diamine
CAS no.	28159-98-0
EINECS no.	248-872-3
Molecular formula	$C_{11}H_{19}N_5S$
Molecular mass	257.37 g/mole
Structural formula	



Cybutryne is manufactured with a minimum purity of 975 g/kg and does not contain (inactive) isomers, additives or relevant impurities.

Physical and chemical properties of the active substance
Cybutryne is (as pure active ingredient) a white cloddy powder with a garlic-like odour. It has a low vapour pressure ($3.4*10^{-5}$ Pa at 25 °C) and a low solubility in tap water (9.0 mg/L at pH 7 and 20°C). The effect of salinity was also investigated at pH 5,7 and 9. A higher salinity results in a significant lower water solubility. Its melting point is 128.4 °C, its boiling point is between 347.3 and 375 °C and its density accounts for 1.11 g/cm^3 at 20 °C (relative density D_4^{20} = 1.11). Its Log P_{OW} (3.1 - 3.2) indicates a potential for bioaccumulation. Cybutryne is regarded as a surface active substance, because the surface tension of a 90% saturated solution is below 60 mN/m.
Cybutryne is not highly flammable, not auto-flammable and does not have explosive properties or oxidising properties.

Methods of analysis
Analysis of the active substance as manufactured
Valid GC-FID methods are available for the determination of cybutryne purity and the content of organic impurities.

Analysis of the biocidal product
A validated HPLC-UV method was provided.

Residue analysis
Soil
Not applicable.

Water

A validated GC-HRMS method was provided, showing cybutryne can be monitored in sea water and drinking water. However, HRMS is currently not considered a commonly available technique. Therefore, at product authorisation, additional validation should be provided, based on a commonly available detection technique.

For surface water, no exposure is expected based on the intended use (use on sea vessels only)

Air
A residue analytical method for air is not required, based on the vapour pressure of cybytryne. However, a validated GC-FID method is available. The LOQ of the method is 0.1 mg/m^3.

Body fluids and tissues
No analytical methods are required to determine the active substance in human body fluids and tissues, as Cybutryne is not classified as toxic or highly toxic.

PT21 specific requirements
A validated GC-HRMS method was provided, showing cybutryne can be monitored in marine sediment, mussels and fish. However, HRMS is currently not considered a commonly available technique. Therefore, at product authorisation, additional validation should be provided, based on a commonly available detection technique.

2.1.2 Intended Uses and Efficacy

The active ingredient Cybutryne present in the biocidal product [redacted]Series is an algicide.[redacted]Series is applied to hulls of ships (commercial deep sea and coastal vessels only >25m in length), in which the active ingredient Cybutryne (2.3%) is an antifoulant against marine algal species causing soft fouling. The active ingredient Cybutryne from [redacted]Series affects the electron transport in the photosystem of algae and plants. This results in reduced CO_2 uptake and decreased carbohydrate production which inhibits the growth in target organisms.
The efficacy of [redacted]Series was shown in a raft test of panels applied with a suitable anti-corrosive primer, a tie coat and [redacted]series as antifoulant. The settlement and growth of marine fouling organisms (in-house method) were determined. Besides, the antifouling performance of [redacted]series applied on a vessel sailing in a heavy fouling area during 34 months is given.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3 Classification and Labelling

Proposed classification for the active substance

Classification	According to Directive 2001/98/EC	According to Regulation 1272/2008
Class of danger	Xi, N	Skin Sens. 1, Aquatic Chronic 1
R phrases	R43, R50/53	H317, H410
S phrases	S24, S37, S60, S61	P273, P391, P501

Proposed classification for the biocidal product

Classification	as in Directive 1999/45/EC	According to Regulation 1272/2008
Class of danger	Xn, Xi, N	Acute Tox. 4, Skin Irrit. 2, Eye Irrit. 2, Skin Sens. 1, Aquatic Chronic 1
R phrases	R10, R20, R36/38, R43, R50/53	H332, H315, H319, H317, H410
S phrases	S36/37, S38, S61	P273, P391, P501

H317: May cause an allergic skin reaction
H332: Harmful if inhaled
H315: Causes skin irritation
H319: Causes serious eye irritation
H410: Very toxic to aquatic life with long lasting effects

P273: Avoid release to the environment
P391: Collect spillage
P501: Dispose of contents/container…(in accordance with local/regional/national/international regulation (to be specified)

Packaging

Suitable container material: high density polyethylene (HDPE) bags and coated steel drums.

2.2 Summary of the Risk Assessment

2.2.1 Human Health Risk Assessment

2.2.1.1 Hazard identification

Toxicokinetics
In table 2.2.1-1 an overview of the toxicokinetics of Cybutryne is given .

Table 2.2.1-1 Summary of Toxicokinetics of Cybutryne in rats

Absorption	From the intestine 87-94%. Systemically available at least 50% at 20/mg/kg, at least 16% at 100 mg/kg. For risk assessment an oral absorption value of 50% will be used.
Distribution	Concentrations were highest in blood and higly perfused organs (lung, hart, spleen, liver kidney and thyroids).
Metabolism	M1 2-S-glucuronide-4-tert-butylamino-6-cyclopropylamino-(1,3,5-triazine) M2 2-S-glutamic acid-4-tert-butylamino-6-cyclopropylamino-(1,3,5-triazine) M3 2-methylthio-4-tert-butyl(-O-glucuronide)amino-6-cyclopropylamino-(1,3,5-triazine) M4 2-S-glycine-4-amino-6-cyclopropylamino-(1,3,5-triazine) M7 2-hydroxy-4-tert-butylamino-6-cyclopropylamino-(1,3,5-triazine)
Excretion	77-93% within 48 hrs; 90-97% within 168 hrs.

Acute toxicity
Cybutryne is of low acute toxicity: LD50 oral rat > 2000 mg/kg bw; dermal rat > 2000 mg/kg bw; LC50 inhalation rat > 4090 mg/m^3 (highest attainable concentration).

Irritation and Corrosivity
Cybutryne is not a skin irritant or an eye irritant.

Sensitization
Cybutryne needs to be classified as a skin sensitizer: R43: 'may cause sensitisation by skin contact' (Directive 67/548/EEC) or with H317:May cause an allergic skin reaction (Regulation 1272/2008/EC), based on a maximization test.

2.2.1.2 Effects assessment

In the sub-acute, semi-chronic and chronic studies in the rat there does not seem to be an effect of prolonging the exposure duration, as the NOAELs are in the same range (7.3, 9.6 and 12.2 mg/kg bw/day respectively).
Within the teratogenicity studies the rabbit is the most sensitive species with a NOAEL of **15 mg/kg bw/day**. This value was chosen as the overall NOAEL as it has the lowest LOAEL (45 mg/kg bw/day) that is higher than the highest NOAEL of all relevant studies. The overall NOAEL can be used for both semi- chronic and chronic exposure, as extending the study-duration did not have a significant effect.
Local effects are only noted in the dietary 1-year dog study and not after dermal exposure.As the dossier concerns an antifouling paint for which oral exposure is considered unlikely, no local AEL is derived.

Genotoxicty and carcinogenicity
Cybutryne is considered to be non-genotoxic and non-carcinogenic

Total assessment factor
A safety factor of 100, i.e. a factor of 10 for inter- and intra-species variation each, is considered sufficient for the AEL derivation of Cybutryne (non-carcinogenic endpoint).
Due to the low absorption of 50% of orally applied doses of Cybutryne, a correction for bioavailability is required.

2.2.1.3 Exposure assessment

The antifouling paint [redacted] Series is applied mainly by high pressure airless spraying. Exposure to the active substance Cybutryne can occur during production and use of the antifouling paint by professionals only. Therefore, exposure is restricted to professionals only (the general public is not exposed). The main routes of exposure are by inhalation and by dermal exposure.

2.2.1.4 Risk characterisation

Based on the expected exposure routes for professional users, the internal dose after dermal and inhalation exposure is calculated taking into account the exposure estimates and the dermal and inhalation absorption. The dermal absorption is determined to be 5% in human skin. As there are no data available on respiratory absorption, the default value of 100% absorption during inhalation exposure will be used. Furthermore, as described above the critical NOAEL is 15 mg/kg bw/day which results in a systemic AEL of 0.08 mg/kg bw/day (equivalent to 4.8 mg/day for a 60 kg operator), using an assessment factor of 100 for intra- and interspecies differences and and a correction for oral absorption of 50%. As a result, the following risk assessment can be performed, based on the AEL approach resulting in a risk index or comparing exposure and toxicity directly resulting in a

Margin of Exposure (MOE). The respective assessments are summarized in table 2.2-2 and table 2.2-3.

Table 2.2.1-2 Risk assessment for dermal and inhalation exposure to Cybutryne for professionals based on AEL-derivation

Route	Estimated internal exposure (mg/kg bw/day)[1]		AEL-systemic (mg/kg bw/day)	Risk-index[2]	
	without PPE	with PPE		without PPE	with PPE
Spray painter (Spraying model 3 (ECB, 2002-User Guidance, 2004))					
Dermal	1.27	0.02[3]	0.08	15.91	0.20
Inhalation	0.02	(0.02)[4]	0.08	0.31	0.31
Total	1.30	0.04	0.08	16.22	0.51
Brush and roller ((1) Consumer product painting model 4 (ECB, 2002-User Guidance, 2004, as modified in 2008, HEEG, 2008))					
Dermal	0.19	0.03[5]	0.08	2.32	0.43
Inhalation	0.00004	(0.00004)[4]	0.08	< 0.01	< 0.01
Total	0.19	0.03	0.08	2.32	0.43
Brush and roller (Links et al., 2007)					
Dermal	0.29	0.001[6]	0.08	3.58	0.01
Inhalation	0.0002	(0.0002)[4]	0.08	< 0.01	< 0.01
Total	0.29	0.001	0.08	3.58	0.01
Potman (Mixing & Loading model 6 (ECB, 2002-User Guidance, 2004))					
Dermal	0.42	0.04[5]	0.08	5.26	0.55
Inhalation	0.003	(0.003)[4]	0.08	0.03	0.03
Total	0.42	0.05	0.08	5.30	0.59
Paint removal (Links et al., 2007)					
Dermal	0.15	0.02[6]	0.08	1.89	0.23
Inhalation	0.02	(0.02)[4]	0.08	0.30	0.30
Total	0.18	0.04	0.08	2.19	0.53
Grit filler (Links et al., 2007)					
Dermal	5.02	0.07[5]	0.08	62.74	0.83
Inhalation	0.02	(0.02)[4]	0.08	0.20	0.20
Total	5.04	0.08	0.08	62.94	1.03

[1] for extrapolation from external exposure to internal exposure for dermal exposure 5 % and for inhalation exposure 100% (default) was used.
[2] Risk index = estimated internal exposure/acceptable operator exposure level
[3] Protective gloves and clothing (double coverall, 1% clothing penetration)
[4] No RPE
[5] Protective gloves and clothing (impermeable coverall, 5% clothing penetration)
[6] Protective gloves and clothing (impermeable coverall, calculation based on actual data values)

Table 2.2.1-3 Risk assessment for dermal and inhalation exposure to Cybutryne for professionals based on MOE-derivation

Route	Estimated internal exposure (mg/kg bw/day)[1]		NOAEL-systemic (mg/kg bw/day)	MOE[2]	
	without PPE	with PPE		without PPE	with PPE
Spray painter (Spraying model 3 (ECB, 2002-User Guidance, 2004))					
Dermal	1.27	0.02[3]	7.5	6	479
Inhalation	0.02	(0.02)[4]	7.5	302	302
Total	1.30	0.04	7.5	6	185

Route	Estimated internal exposure (mg/kg bw/day)[1]		NOAEL-systemic (mg/kg bw/day)	MOE[2]	
	without PPE	with PPE		without PPE	with PPE
Brush and roller ((1) Consumer product painting model 4 (ECB, 2002-User Guidance, 2004, as modified in 2008, HEEG, 2008))					
Dermal	0.19	0.03[5]	7.5	40	216
Inhalation	0.00004	(0.00004)[4]	7.5	208696	208696
Total	0.19	0.03	7.5	41	216
Brush and roller (Links et al., 2007)					
Dermal	0.29	0.001[6]	7.5	26	9904
Inhalation	0.0002	(0.0002)[4]	7.5	37267	37267
Total	0.29	0.001	7.5	26	7825
Potman (Mixing & Loading model 6 (ECB, 2002-User Guidance, 2004))					
Inhalation	0.42	0.04[5]	7.5	18	170
Dermal	0.003	(0.003)[4]	7.5	2746	2746
Total	0.42	0.05	7.5	18	160
Paint stripping (Links et al., 2007)					
Dermal	0.15	0.02[6]	7.5	50	402
Inhalation	0.02	(0.02)[4]	7.5	311	311
Total	0.18	0.04	7.5	43	175
Grit filler (Links et al., 2007)					
Inhalation	5.02	0.07[5]	7.5	1.5	114
Dermal	0.02	(0.02)[4]	7.5	461	461
Total	5.04	0.08	7.5	1.5	91

[1] for extrapolation from external exposure to internal exposure for dermal exposure 5 % and for inhalation exposure 100% (default) was used.
[2] MOE = internal NOAEL/estimayed internal exposure
[3] Protective gloves and clothing (double coverall, 1% clothing penetration)
[4] No RPE
[5] Protective gloves and clothing (impermeable coverall 5% clothing penetration)
[6] Protective gloves and clothing (impermeable coverall, calculation based on actual data values)

Based on this risk assessment, it is concluded that respiratory and dermal exposure of professional users to antifouling paint containing 2.3 % Cybutryne may lead to adverse health effects when no PPE is used. However, when using gloves and double coverall for spray painting or gloves and impermeable coverall for brushing and rolling, paint stripping and for potmen, no adverse health effects are expected. For the grit filler, a risk index of 1.03 and a MOE of 91 was identified for the exposure calculations including gloves and impermeable coverall. For the exposure calculations many worst-case approaches and assumptions had to be used: dermal absorption based on *in vivo* rat study, worst-case assumption on the active substance present in paint to be removed, 90th percentile exposure values (as 75th were not available at time when calculations were performed). Therefore, the slight exceeding values are considered due to the worst-case exposure calculations and therefore no adverse health effects are expected for the protected (gloves and impermeable coverall) grit filler. Exposure of the ancillary worker is covered by the exposure calculations of the spray painter. Therefore, no adverse health effects are expected after respiratory and dermal exposure to cybutryne of the protected (gloves and impermeable coverall) ancillary worker.

Access of unauthorised personal to professional shipyards is considered to be unlikely. At TMIII 2011 it was agreed that a specific bystander exposure scenario was not necessary to include into CA/reports on active substances in antifouling products. To keep unauthorised persons from entering the treatment

area, the product label should carry the phrase "Unprotected persons should be kept out of treatment areas".

Based on the environmental exposure assessment, no relevant residues are expected in matrices for human consumption (drinking water or fish/seafood; see section 3.3.6 and 3.3.8). Although not considered relevant, a reverse reference scenario was performed to calculate the amount of fresh fish eaten by a person every day of his life before filling up the ADI.

An ADI could be derived using the NOAEL of 15 mg/kg bw/d based on the teratogenicity study in rabbit and an assessment factor of 100, resulting in an ADI of 0.15 mg/kg bw/day.
Using a body weight of 60 kg for a person, a person can be exposed to 9 mg or 9000 µg cybutyne a day for a lifetime.

Using the PEC value for secondary poisoning:

$$\mathbf{PEC_{oral,\ predator} = PEC_{harbour,water} \times BCF_{fish} \times BMF = 0.421/2 \times 250 \times 1 = 52.6\ \mu g\ a.s./kg_{wet\ fish}}$$

Using a reverse reference scenario, one can eat 9000/52.6 = 171 kg wet fish a day for a lifetime.
This is value is considered to be worst-case for shellfish as the value for wet fish is considered for a fish containing 5% fat (in which Cybutryne could potentially accumulate).

2.2.2 Environmental Risk Assessment

2.2.2.1 Fate and distribution in the environment

Cybutryne is not readily biodegradable, and also the abiotic degradation of Cybutryne in seawater is very slow. In studies present in the dossier, no significant mineralization was observed. The dissipation from seawater to sediment in a microcosm study however was found to be fast (DT_{50}: 23 days). The half-life in the water column of the major degradation product of Cybutryne in marine waters, GS 26575, is comparable to the parent compound (DT_{50}: 23 days). Cybutryne and its primary metabolite GS 26575 showed to be recalcitrant to biodegradation. No reliable degradation rates are available for the sediment compartment or the whole system, therefore the DT50 of the marine aquatic system was set to infinite.
Based on the average K_{OC}-value of 895 L/kg for adsorption, Cybutryne is classified as having a low mobility potential in soil. Cybutryne's sorption characteristics in combination with its recalcitrance towards biodegradation pose a risk for accumulation to be assumed in plants and sediment.
Cybutryne has a moderate potential to accumulate in fish (BCF 250 L/kg), but is eliminated fast ($t_{1/2}$ < 3 days). Although, the accumulative potential in macro algae was relatively high (BCF 5200 L/kg), the elimination of Cybutryne was also fast for this species ($t_{1/2}$ 9.2 days). The bioconcentration in a microcosm test demonstrated that Cybutryne does not bioconcentrate in periphyton, rooted plants and macro invertebrates, and that biomagnification does not play a significant role. The highest BCF_{SS} values for invertebrates were 110 L/kg ww for oyster (*Crassostrea virginica;* suspension feeder) and 307 L/kg ww for amphipods (*Leptocheirus plumulosus*; surface deposit feeder). The latter value can be taken as an indication that food-chain transfer resulting in biomagnification is not an apparent concern, since the BCFs in algae and plants were below the 2000 L/kg ww trigger (max. 1397 L/kg) and higher than the BCFs in the herbivorous organisms.

2.2.2.2 Effects assessment

Aquatic compartment

The effect assessment of the aquatic compartment consists of a discussion on the pooling of data on marine and freshwater organisms, evidence for potential endocrine disruption and on PNEC derivation.

Pooling data

Regarding the use of freshwater and/or marine data, the TGD (4.3.1.2 Evaluation of data) states: 'The use of freshwater acute effects data *in lieu* of or in addition to saltwater effects data for risk assessment purposes is not contra-indicated by the empirical data reviewed. Use of pooled data is therefore recommended. Under such circumstances, PNEC values should be derived from the most sensitive endpoint regardless of the medium.' Additionally at TMI08 it was concluded that 'for the derivation of a PNEC for freshwater or saltwater the available toxicity data for freshwater and saltwater organisms can be pooled. Before pooling these data the differences in sensitivity has to be considered: in general if the difference is more than a factor 10 the data cannot be pooled. In addition, the mode of action of the substance under evaluation has to be considered.'

Mode of action

The toxicity data with species from different phyla indicate that the primary producers, i.e. algae and aquatic macrophytes, are the most sensitive group of aquatic species. Since the mode of toxic action of Cybutryne, like other triazine herbicides, is the inhibition of photosynthetic electron transport, this could be expected. The inhibition of the photosynthetic activity occurs in photo-system II (PSII), where the incorporation of CO_2 in organic molecules is inhibited, ultimately leading to an inhibition in growth.

Cybutryne as a triazine algicide is known to inhibit photosynthesis. This is in line with the observation that primary producers (algae and aquatic macrophytes), were the most sensitive aquatic species. The active substance, however, appeared to be also highly toxic to fish and invertebrates. The mode of action in these organisms is, nevertheless, unknown. There is no reasoning available to assume that the working mechanism in freshwater and marine should be considered as different.

Differences in sensitivity

The RMS has tried to make a comparison of freshwater and marine ecotoxicity data . Additionally PNEC values were calculated on basis of freshwater, marine ecotoxicity data. At TM III 2011 it was considered that the results from Higher Tier test results could not be used to determine the (non) pooling of data.

A summary of the endpoints for the most susceptible standard species tested in freshwater and marine toxicity tests with the active substance Cybutryne is presented in Table 2.2.2-1.

Table 2.2.2-1 Freshwater and seawater aquatic toxicity data Cybutryne

Test type	Freshwater	Exposure		Endpoint		Marine	Exposure		Endpoint	
	Test species	Design	Duration	Type	µg a.s./L	Test species	Design	Duration	Type	µg a.s./L
Fish acute	*Oncorhynchus mykiss*	F (n)	96 h	LC_{50}	860	*Menidia beryllina*	S (mm)	96 h	LC_{50}	1760
Aquatic invertebrates acute	*Daphnia pulex*	S (n)	24 h	EC_{50}	5700	*Mysidopsis bahia*	S (n)	96 h	EC_{50}	480
Aquatic invertebrates chronic	*Daphnia magna*	F (mm)	21 d	NOEC	510	*Mysidopsis bahia*	F (mm)	28 d	NOEC	110
Aquatic inverte. chronic – Number embryos	*Potamopyrgus antipodarum*	R (n)	56 days	NOEC	<0.05	-	-	-	-	-
Aquatic inverte. chronic – Number eggs	*Lymnaea stagnalis* *	R (twa)	56 days	NOEC	≥117	***Ilyanassa obsoleta***	-	45 d	NOEC	1500
Algae growth inhibition	*Navicula pelliculosa*	S (twa)	72 h	EC_{50}	1.47	*Skeletonema costatum*	-	96 h	EC_{50}	0.17
			72 f	EC_{10}	0.02				NOEC	0.022

Aquatic macrophytes	*Lemna gibba*	S (m)	14 days	EC_{50} NOEC	1.65 0.671	*Ruppia maritima*	-	28 days	EC_{50}	0.843
Fish Growth / chronic ELS	*Oncorhynchus mykiss*	F (mm)	95 days	NOEC	4	*Cyprinodon variegatus*	F (mm)	33 d	NOEC	170
Sediment dwelling organisms	*Chironomus riparius*	Spiked water – S gm	28 days	NOEC	≥30.3 (>1.2 [mg/kg dw])	*Ampelisca abdita*	Spiked sediment – SS (mm)	10 days (acute)	NOEC	44 [mg/kg dw]
Additional marine taxonomic groups										
Coral - Cnidaria						*Seriatophora hystrix*		10 h	EC_{50}	0.7
Coral - Cnidaria						*Acropora formosa*		10 h	EC_{50}	0.9
Ascidia - urochordata (sea squirt)						*Ciona intestinalis*		24 h	EC_{50}	2.11
Echinodermata						*Paracentrotus lividus*		48 h	EC_{50}	6.03

* Discussed further in the section on endocrine disruption
n = nominal; mm = mean measured
F = flow-through; R = renewal; S = static

In standard laboratory tests the lowest 72-h EC_{10} for Cybutryne was observed with the freshwater diatom *Navicula pelliculosa* (NOEC = 20 ng a.s./L), while marine diatoms are similarly susceptible: 96-h NOEC 22 ng a.s./L. It is concluded that Cybutryne is highly toxic for primary producers but less toxic towards non-photosynthetic aquatic organisms, such as fish and invertebrates (NOEC 4-510 µg/L) (with the exception of freshwater snails (*Potamopyrgus antiporum*). It can be seen from Table 2.2.2-1 that the sensitivity difference between freshwater and marine species is > 10 for aquatic invertebrates (both acute and chronic), in the chronic fish studies and chronic snail studies. However, given the mode of action of cybutryne and the fact that freshwater and marine primary producers are the most sensitive species and have a similar sensitivity, it is proposed to pool the freshwater and marine ecotoxicity data. At TM I 2012 this was discussed and agreed upon as a way forward.

Acute toxicity data for fish invertebrates and algae are available for metabolite [redacted] The lowest values were found for the marine algae *Skeletonema costatum* with an EC50 of 16 ug/L and the freshwater algae *Navicula pelliculosa* with an EC50 of 190 µg/L. Both endpoints, however, are based on 120 hour tests and thus do not comply with the requirement of exponential growth. A comparison between the active substance and metabolite [redacted] of tests with the same species is given in Table 2.2.2-2. From this comparison it is not possible to conclude that [redacted] is less or more toxic than the active substance.

Table 2.2.2-2 Comparison ecotoxicity of metabolite [redacted] with cybutryne.

			Cybutryne		[redacted]	
Species	Effect parameter	Duration	EC_{10} (µg/L)	L(E)C50 (µg/L)	EC_{10} (µg/L)	L(E)C50 (µg/L)
Daphnia magna	Mortality / acute	48-h		**8.3** and 2.4		**11**
Skeletonema costatum	Growth inhibition	120-h	**0.146**	*0.452*	**0.18**	*16*
Daphnia pulex	Mortality / acute	24-h		*5.7*		*27*
Navicula pelliculosa	Growth inhibition	120-h	*<0.0756*	*0.0957*	*<77*	*190*

In **bold**: test results showing similar toxicity. In *Italic*: test results showing that [redacted] is less toxic than cybutryne. Please notice 120 h endpoints are only included for comparative reasons.

Short term dietary toxicity tests showed low acute toxicity of Cybutryne (5 days LD_{50} of >5620 and >2000 mg a.s./kg food) towards birds and mammals. Sub chronic exposure of rats gave a 90 days NOEC of 150 mg a.s./kg food.

Conclusion
At TMI08 it was concluded that 'for the derivation of a PNEC for freshwater or saltwater the available toxicity data for freshwater and saltwater organisms can be pooled. Before pooling these data the differences in sensitivity has to be considered: in general if the difference is more than a factor 10 the data cannot be pooled. In addition, the mode of action of the substance under evaluation has to be considered.' On basis of information on mode of action there are no reasons not to pool freshwater and marine data. At TM I 2012 this was discussed and agreed upon as a way forward.

Endocrine disruption
A higher tier freshwater study was supplied to the RMS by the German Competent Authority. As the authors in this study concluded that Cybutryne has an endocrine disruption potential, the study was summarised / evaluated by the RMS and included in doc IIIA section A7.4.3.5/04). In addition to the report some raw data were submitted by the UBA (Federal Environmental Agency, producer of the study report). These data have been taken into consideration. The authors of the report, however required confidentiality of the raw data, therefore no summary of the confidential data is included.
In the indoor freshwater mesocosm study, fauna and flora naturally present in highly eutrophic but uncontaminated sediment from a lake near Brandenburg were treated once with Cybutryne at a nominal concentration of 0.04, 0.2, 1 and 5 µg a.s./L. Since chemical analysis showed dissipation of the active substance (less than 8% remained in the water column after 147 days), it was considered appropriate to use TWA (Time Weighted Average) concentrations. The corresponding TWA concentrations are 0, 0.006, 0.031*, 0.211and 1.425* µg/L (*=average of 2 replicate systems).
The authors indicated that Cybutryne (and eventually its main metabolite GS 26575) may induce endocrine effects such as in snails and other invertebrates.

The endocrine effects of Cybutryne on the freshwater snail *Radix balthica* sampled from the indoor freshwater mesocosms were described in a separate study in more detail (see section A7.4.3.4/05). Endocrine disrupting effects in ***R. Balthica*** between controls and Cybutryne-treated mesocosms were evaluated using appropriate univariate and multivariate statistical methods. The authors calculated EC_{10} -values, that are based upon nominal and TWA-based concentrations, of the different endpoints. Applying regression analysis a lowest $EC_{10,nominal}$ of 0.032 µg/L at day 60 (EC_{10} TWA 0.014 µg/L) was derived for the parameter spermatogenesis and a EC_{10},nominal of 0.057 µg/L at day 60 (EC_{10} TWA 0.025 µg/L) for the parameter albumen gland hypertrophy.

The applicant commented the study on endocrine disruption and concluded in summary the following: "The reliability of the studies on *Radix balthica* and ***A. aquaticus*** is considered to be low, and it cannot be concluded that the observed effects were directly caused by Cybutryne, let alone that they were the result of endocrine disruption. This does not necessarily imply that Cybutryne is incapable of causing a reduction in the reproductive success of these organisms through an endocrine disrupting mode of action, although this seems unlikely on the available evidence, but further work would be needed to demonstrate such effects in a reliable manner". Additionally the applicant provided a (not evaluated) in-vitro test (estrogen Yeast assay), which does not indicate a potential for endocrine disruption.

In response the authors of the *R.balthica* study report indicated the following: our data cannot and do not proof that Cybutryne is an endocrine disrupter in ***Radix.*** A proof in the strict sense is not possible because there are neither agreed specific endpoints for endocrine disruption in invertebrates nor standardised tests. However, it is also clear that Cybutryne exhibits a strong reproductive toxicity in *Radix* and the specificity of these effects on male reproductive organs, spermatogenesis – in both cases an inhibitory effect – and the stimulating effects on female reproductive organs point to a potential endocrine-mediated effect of Cybutryne in *R.balthica*. The discussion amongst scientists concerning the *Radix baltica* is added in doc IIA, Appendix 1. The RMS agrees with the applicant that no

thorough statistical analysis was included in the mesocosm and *R. balthica* study reports and that it was not possible to carry out such an analysis on basis of the limited raw data submitted in addition..

As a follow up, the applicant has provided an evaluated chronic reproduction study with the freshwater pond snail *Lymnaea stagnalis* which demonstrated that pulmonate molluscs such as *L. stagnalis* are not particularly sensitive to Cybutryne.
The pond snail is one of the recommended test species in a detailed review paper on mollusc (partial) life-cycle toxicity testing (OECD, 2010).
Using *L. stagnalis* enables to follow the complete reproductive output and thereby to detect all possible effects. Over the course of 56 days the snails were exposed to a wide range of concentrations (0.24 µg/l to 150 µg/l). To maintain constant exposure over time the medium was renewed completely every 7 days. Further a partly renewal 3 days after completely renewal was necessary to maintain the concentrations. Applying one way analysis of variance (ANOVA) a NOEC for reproduction of ≥ 150 µg/L, corresponding with a $NOEC_{TWA}$ of ≥ 117 µg/L.
No effect on growth or on reproduction was observed during the exposure period, demonstrating that pulmonate molluscs such as *L. stagnalis* are not particularly sensitive to Cybutryne.

Furthermore, a chronic reproduction study with the freshwater mudsnail *Potamopyrgus antipodarum* is submitted by the UBA. The mud snail is also a candidate species in a detailed review paper on mollusc (partial) life-cycle toxicity testing (OECD, 2010)..
Ten snails per replicate were sampled and analysed on day 28 of the experiment and all surviving snails per replicate on day 56. As endpoints mortality and the number of embryos in the brood pouch of females were recorded, distinguishing shelled and unshelled embryos
From the study it was concluded that Cybutryne caused a significant increase of total embryo numbers in all exposure groups after 4 and 8 weeks, including the lowest concentration (0.05 µg/L). Also the number of embryos without shell increased under Cybutryne exposure, although this effect was only significant in a concentration window between 0.13 and 0.8 µg/L after 4 weeks and between 0.05 and 0.8 µg/L after 8 weeks. This increase attained factor 4 at 0.13 µg/L after 8 weeks for the total embryo number and was therefore comparable in intensity to the increase observed under exposure to the known xeno-estrogens Bisphenol A and Ethinylestradiol (EE2).
The concentration-response relationship for Cybutryne resembled an inverted U as described in several other studies with xeno-estrogens.
However, it must be noted that the test addresses the assessment of hormonally active substances but is not exclusively sensitive to EDCs and is equally suitable for the detection of adverse effects on reproduction mediated via other modes of action. This is in line with the following information given in the discussion of the study report: ‘’there is currently no convincing explanation for the molecular mechanism by which Cybutryne may act as a xeno-estrogen in *P. antipodarum’’*. Furthermore, a no effect concentration (EC_{10} or NOEC) was not derived for the endpoints studied, only a LOEC of 0.05 µg/L.

In general it can be concluded that no distinct reproductive effects of Cybutryne were observed in the chronic laboratory studies with snail species and in the higher tier mesocosm studies that firmly can be related to a endocrine mode of action of Cybutryne. The xeno-estrogenic effects of Cybutryne observed, however, are similar to known endocrine disrupters such as Bisphenol A and Ethinylestradiol, the molecular mode of action is, however, unknown. There is insufficient evidence to identify Cybutryne as an endocrine disrupter, but the information available is considered sufficient to identify Cybutryne as ‘potential’ endocrine disrupter.
It is at present not fully clear what the ecological relevance is of observed effects in snails. It is suggested that an increasing reproduction as induced in the current investigation in the freshwater mudsnail by Cybutryne is not beneficial for the population. Estrogenic chemical exposure of females out of the breeding season leads to a stimulation of reproduction, which ultimately may cause a rupture of the oviduct. Furthermore, this stimulation is likely to cause energy shortages in growth, maintenance and reserves. When exposure occurs out of season, offspring will encounter unfavourable circumstances in the outside world (e.g. sub-optimal temperatures, lack of food and hiding places).

Estrogenic chemical exposure of females in the breeding season could to a reduced reproductive performance, which ultimately reduces the number of offspring during the most favourable time for juvenile growth and survival in the environment. Whether these adverse effects indeed occur under field conditions is unknown.

It should also be kept in mind that invertebrate endocrine systems are different from those in vertebrates. In a 2 generation reproduction study with rats and two development toxicity studies with rats and rabbits no endocrine disruptive effects were observed. At TM I 2012 it was agreed that the *P.antipodarum* study cannot be discarded for the risk assessment, but that the study results do not provide evidence to identify Cybutryne as (potential) endocrine disrupter. It was agreed that more research is needed to finalise this discussion.

PNEC for freshwater and marine organisms

Combining freshwater and marine toxicity data it is shown that algae are the most sensitive taxonomic group with an E_rC_{10} of 0.020 µg/L for the freshwater algae *Navicula pelliculosa* and a NOEC of 0.022 µg/L for the marine algae *Skeletonema costatum*. The dossier submitted by the applicant contained too few taxonomic groups to apply the SSD method. Incorporating the data from the EQS report, which was prepared as part of the water framework directive, gives room to carry out a more comprehensive PNEC derivation. Complicating factor, however, is the test result for the freshwater snail *Potamopyrgus antipodarum* with a NOEC <0.05 µg/L. In this test a non-linear dose effect relationship was observed, but only an inverted U-shaped dose response curve was obtained, making it impossible to derive/extrapolate a NOEC from this study. At TM II 2012 it was agreed that this study could not be discarded and should be part of the uncertainty analysis in deriving the PNEC.
Other chronic marine NOEC data available are for fish, algae, crustaceans and snails. Chronic freshwater data are available for fish, algae, crustaceans, snails (sensitive and non-sensitive species), and freshwater plants.

It was tested whether note d to Table 25 in the TGD is applicable stating that "The assessment factor may be reduced to a minimum of 10 in the following situation:
− where short-term tests for additional species representing marine taxonomic groups (for example echinoderms or molluscs) have been carried out and indicate that these are not the most sensitive group, and it has been determined with a high probability that long-term NOECs generated for these species would not be lower than that already obtained;"

Next to acute tests with other marine taxonomic groups two short term tests of 10 hours exposure with Cnidaria (coral) are available showing EC_{50} values in the range of 0.7 to 0.9 µg/L (Table 2.2.2-1). From the same study also one 24 h EC_{50} value was derived in the range of 1.3 µg/L. Additionally the acute to chronic ratio (ACR) was estimated for the different photosynthetic species this ratio was between 1 and 12. If the highest ACR is applied to the lowest EC_{50} of 0.7 µg/L this results in a NOEC/EC10 of 0.06 µg/L. From this analysis can be concluded with a high probability that long-term NOECs generated for Cnidaria would not be lower than that already obtained. There is thus sufficient evidence to lower the assessment factor for the marine environment.

In line with the TGD the assessment factor of 10 is justified for both freshwater and the marine by the fact that long-term NOECs from at least three species representing three trophic levels (fish, aquatic invertebrates and algae) are available, but that chronic NOECS for marine taxonomic groups such as echinoderms and molluscs are missing. Using the studies for PNEC derivation from pooled data on fish, aquatic invertebrates and algae results in:

$PNEC_{water}$ = 0.02 µg a.s./L / 10 = 0.002 µg a.s./L = 2.0 ng a.s./L

The question comes up whether further refinement of the assessment factor is possible on basis of all the information available. In the EQS document a SSD analysis was performed for primary producers resulting in a HC5 of 7.61 ng/L. In the EQS document the following approach was chosen to derive the assessment factor: "According to the TGD-EQS a default assessment factor of 1-5 has to be

applied on the SSD. An assessment factor of 3 is chosen. The reason for this is that although the SSD was made for the most sensitive taxonomic group, and the data distribution is very even, the SSD consists of less than the recommended 15 data points (Commission of the European Communities 2010). Hence, the statistical uncertainty should be judged higher than the statistical fit suggests. Based on the HC5 of 7.61 ng/L and an assessment factor of 3, an AA-QS (SSD) of 2.5 ng/L results."

The following reasoning is considered relevant for not lowering the assessment factor:

1. The TM II 2012 did not agree on lowering the AF further on the basis of the findings of the mesocosm studies. Reasoning is that the dosing regime is different from the exposure situation, which for antifoulings, represents a constant exposure. Moreover, results from the chronic mesocosms studies listed in the EQS document show high toxicity also in these tests. The lowest NOEC freshwater is 4 ng/L (Nyström et al. 2002) and the lowest marine NOEC is 16 ng/L (Dahl and Blanck, 1996), showing similar ecotoxicity compared to the lowest freshwater algae EC10 of 20 ng/L in a standard laboratory study.
2. The SSD on primary producers as applied in the EQS report is considered not appropriate because insufficient chronic data are available for representative taxonomic groups.
3. The EQS report did not have information of the freshwater snail study (NOEC <50 ng/L). This LOEC is close to the lowest NOEC from algae (20 ng/L) and lowering the assessment factor may result in a underestimation of the PNEC when taking into account adverse effects for snails. The TM II 2012 agreed that this should not be discarded.

PNEC water of major metabolite [redacted]
Acute toxicity data for fish invertebrates and algae are available for metabolite [redacted] The lowest values were found for the marine algae *Skeletonema costatum* with an EC50 of 16 ug/L and the freshwater algae *Navicula pelliculosa* with an EC50 of 190 µg/L. Both endpoints are based on 120 hour tests and thus do not comply with the requirement of exponential growth. It is therefore not possible determine separate PNECs for [redacted] nor to conclude that [redacted] is less or more toxic than the active substance. The relatively high assessment factors used for the PNECs of active substance, however, are considered sufficiently protective also for the metabolite.

PNEC sediment
Considering that the results from the freshwater and marine sediment tests differ by more than a factor of 10 it was agreed at TM II 2012 that the data could not be pooled for PNEC derivation. In the EQS dossier, however, a study with the brackish-freshwater amphipod *Monoporeia affinis* is included. The result from this study could be used for both marine and freshwater PNEC derivation. Additionally it was noted that next to the PNEC based on assessment factors also a equilibrium partitioning (EPM) PNEC should be derived.

One chronic **water-spiked** freshwater-sediment study is available. The chronic toxicity of Cybutryne in water for the midge *Chironomus riparius*, resulted in a NOEC of >1.2 mg/kg dw (> 0.24 mg/kg ww).
applying an AF of 100 results in:

$PNEC_{freshwater\ sediment}$ = 240/100 = 2.4 µg a.s./kg (wet weight) 12 µg a.s./kg (dry weight)
= 2.4 ng a.s./g (wet weight) 12 ng a.s./g (dry weight)

As is stated in the TGD: available sediment tests should be carefully evaluated. "Special attention should be given to the pathways through which the test organisms are exposed to the chemical and the test protocol should carefully be checked, whether feeding with unspiked food has possibly reduced exposure via sediment ingestion." It was noted in the test that there was an excessive feeding of > 1 mg/larvae/day instead of recommended 0.25 in first 10 days and it cannot be determined whether this may have lowered the toxicity. Considering that it cannot be ruled out that excessive feeding has influenced the toxicity this PNEC can only be used for comparative reasons.

In the EQS dossier one sediment study is available with the brackish-freshwater amphipod *Monoporeia affinis*, indicating a 24h EC_{50} of 40 µg/kg dry weight for reduced burial in sediment. The result from this study shows that the results from chronic tests do not preclude (short term) sublethal

effects. In this report this test result was used for EQS derivation (0.040 µg/kg dry weight) applying an assessment factor of 1000 (acute test for freshwater). Using *Ampelisca abdita* endpoint for PNEC derivation from pooled data for freshwater and marine sediments results in:

$PNEC_{sediment}$ = 40/1000 = 0.040 µg a.s./kg (dry weight)

PNEC on basis of equilibrium partitioning

As only limited information is available on the toxicity of Cybutryne for sediment dwelling organisms additionally the $PNEC_{sed}$ is calculated from the $PNEC_{water}$ (2.0 ng a.s./L), using equilibrium partitioning. This results in a $PNEC_{sediment\ EPM}$ of 0.19 µg/kg dry weight (0.041 µg/kg wet weight). Please note that the $PNEC_{sediment}$ based on equilibrium partitioning, which includes sensitive photosynthesising species, is higher than the PNEC derived from the amphipod *Ampelisca abdita*. This supports the conclusion that an assessment factor of 1000 is sufficient protective. Furthermore, considering that the assessment factor for the freshwater and marine water compartment was set equal, this supports that also for the sediment that the assessment factor is set equal.

For other antifoulings (TM IV 2011) the TM agreed to use the lowest PNEC if it is known that not the most sensitive species is tested (in this case the $PNEC_{sublethal\ effects}$). Therefore for the risk assessment the following $PNEC_{sediment}$ value is used:

$PNEC_{sediment}$ = 0.040 µg/kg dry weight (ng a.s./g dry weight)

This PNEC is considered relevant for concentrations in sediment, freshly deposited sediment and suspended matter.

PNECsediment for metabolite [redacted]

No separate PNEC sediment could be determined. See explanation above on PNECwater for metabolite [redacted]

PNEC for STP micro-organisms

According to the TGD, the PNEC for micro-organisms in sewage treatment plants can be determined by application of AF 10 on the NOEC derived in an activated sludge growth inhibition test. In the available test, no adverse effects of Cybutryne on the micro-organism population of an activated sludge was found at concentrations of up to and including 1,000 mg a.s./L (= NOEC) resulting in:

$PNEC_{STP}$ = 100 mg a.s./L

Considering that the NOEC value is above the maximum water solubility of 9 mg/L, it is additionally proposed to use the maximum solubility as PNEC:

$PNEC_{STP,solub}$ = 9 mg a.s./L

PNEC for soil organisms

No direct emissions to soil or groundwater are expected from the use of Cybutryne in antifouling products for commercial coastal and ocean-going vessels. Therefore no data for the terrestrial compartment was available, on basis of the PNEC for aquatic organisms the PNEC for terrestrial organisms was calculated using the equilibrium partitioning method (EPM) to the $PNEC_{freshwater}$ of 2.0 ng/L.

$PNEC_{soil\ EPM}$ = 0.036 µg/kg dry weight (0.032 µg/kg wet weight)

PNEC for the air compartment

No direct emissions to air are expected from the use of Cybutryne in antifouling products for commercial coastal and ocean-going vessels. Therefore no data for the air compartment was available, and the PNEC was not calculated.

PNEC for secondary poisoning

Sea birds might be exposed to Cybutryne residues preying on marine biota. For birds no long-term reproduction study is available. Data on the toxicity of Cybutryne to birds were generated in acute and short-term toxicity tests with standard test species which will be used as surrogate for sea birds. The LC_{50} value from one short-term dietary test is available (5,620 mg a.s./kg food) and therefore an AF of 3,000 has to be applied resulting in:

$PNEC_{oral\ bird}$ = 5,620/3,000 = 1.87 mg a.s./kg food
1870 µg a.s./kg food

The main path of Cybutryne entry into the environment is via leaching of the active substance during the service life of antifouling paint. Thus, the dominant receiving compartment will be sea water.

Seals might be exposed to Cybutryne residues preying on marine biota. Data on the long-term toxicity of Cybutryne to mammals were generated in toxicity tests with standard test species (rodents) which will be used as surrogate for marine mammalian species.

The NOEC-value (150 mg a.s./kg food) from a 90-day sub-chronic feeding study with rat is available. The assessment factor for the subchronic rat study is 90 according to the TGD, which accounts for laboratory to field and subchronic to chronic extrapolation, resulting in:

$PNEC_{oral\ mammal}$ = 150/90 = 1.67 mg a.s./kg food
= 1670 µg a.s./kg food

Overview of predicted no effect concentrations (PNECs)
As presented above Predicted No Effect Concentrations have been derived. An overview is given in table 2.2.2-2.

Table 2.2.2-2 Overview of predicted no effect concentrations (PNECs)

Compartment		Predicted No Effect Concentrations	
Water	$PNEC_{fwater}$	2.0	(ng a.s./L)
Sediment	$PNEC_{sediment\ /\ freshly\ deposited\ sediment\ /\ suspended\ matter}$	0.040	(ng a.s./g dw)
Terrestrial	$PNEC_{soil\ EPM}$	0.036 0.032	(µg a.s./kg dw) (µg a.s./kg ww)
Air		Not determined	
Waste water treatment	$PNEC_{STP}$	100 (9)*	(mg a.s./L)
Secondary poisoning	$PNEC_{oral,\ mammal}$	1870	(µg a.s./kg food)
	$PNEC_{oral,\ bird}$	1670	(µg a.s./kg food)

*: PNEC value between brackets is based on maximum water solubility

2.2.2.3 PBT assessment

Cybutryne fulfils the criteria for Persistence and Toxicity, but not for Bioaccumulation in fish. Cybutryne is not readily biodegradable according to OECD criteria. Additionally, higher tier tests in freshwater and marine water are available. No significant degradation of Cybutryne was found (DT50 > study duration of 12 month). However, the dissipation from seawater was investigated in an outdoor microcosm under natural climatic conditions. Cybutryne dissipated from the microcosm water under the actual test conditions with a DT50 of approximately 22.5 days. [redacted] was the only metabolite found in the test system peaking at a maximum concentration of 150 ng a.s./L after one month, then declining with approximately the same half-life as Cybutryne (22.7 days).
In a freshwater microcosm Cybutryne dissipated from the microcosm water under the actual test conditions with a half-life of approximately 35 days. [redacted] was the only metabolite found in the

test system. No DT50-values for [redacted] in the water phase and Cybutryne in the sediment could be calculated since the dataset was too small. Due to the data in the microcosm studies Cybutryne is regarded as persistent. Cybutryne does not biodegrade in marine sediment. On basis of the available studies, however, it is not possible to establish half-lives and thus to properly address the P-criterion. Therefore, the cybutryne , and should therefore be considered as potentially persistent (P)/very persistent (vP).

Cybutryne does not bioconcentrate in fish (BCF = 250 L/kg) in a OECD 305E test, but the accumulative potential in macro algae was relatively high (BCF 5,200 L/kg) with a elimination half life of Cybutryne 9.2 days. In a microcosm test is demonstrated that Cybutryne does not bioconcentrate in periphyton, rooted plants and macro invertebrates. Please notice that only tests with fish (OECD 305) and mussels (ASTM E1022-94 (if available) directly can used for comparison with the B and vB criteria (ECHA guidance document r11 page 25). BCF values determined in other invertebrates (e.g. algae) should not be used, since they are prone to high uncertainty due to adsorption (ECHA guidance document R 7C), On the other hand also substances adsorbed on e.g. algae may result in bioaccumulation and biomagnification in higher trophic levels. The microcosm study A7.4.2-02, however, shows highest BCFSS values of 110 L/kg ww for oyster (*Crassostrea virginica*; suspension feeder) and 307 L/kg ww for amphipods (*Leptocheirus plumulosus*; surface deposit feeder). The latter values can be taken as an indication that food-chain transfer resulting in biomagnification is not an apparent concern, since the BCFs in algae and plants were below the 2000 L/kg trigger (up to 1397 L/kg) and higher than the BCF in herbivorous organisms. Cybutryne is therefore not regarded as bioaccumulative.
Cybutryne is thus not classified as a PBT or vPvB substance. However, potentially two of the three criteria (P and T) are fulfilled. Which means that the active substance potentially meets the criteria for substitution of Article 10(1) of the Biocidal Products Regulation 528/2012 (BPR) and is identified as a potential candidate for substitution.

2.2.2.4 Exposure assessment

The EU risk assessment procedure for biocides should consider the full lifecycle of the product including: manufacture, formulation, professional and private uses, and service life and disposal. The potential impact on all relevant environmental compartments should be considered. Since Cybutryne is manufactured outside the EU, this stage in the lifecycle will not lead to environmental exposure in Europe. The formulated product [redacted] Series is manufactured in Europe at facilities operated by [redacted] at which extensive measures are taken to prevent release of the active substance into the environment. Storage and production take place on floors that are disconnected from the sewer. As an additional safety measure, a buffer tank is installed in the sewer of the internal transport system: any accidental spillages are held back, and transported to certified hazardous waste treatment facilities. No significant environmental release is therefore expected from manufacture of the formulated product.

Use of Cybutryne containing antifouling paints is restricted by the applicant to commercial marine vessels (non-pleasure vessels). Therefore expected routes of environmental exposure are limited to releases into marine waters in either harbours, the wider environment, shipping lanes or open sea. The main routes of entry into the environment is *via* leaching of the active substance during the service life and *via* discharge from docks or marine lift as a result of application and removal of antifouling. Thus the dominant receiving compartment will be sea water.

<u>Calculation of emissions to marine waters:</u>

- Service life
  - commercial harbour
  - wider environment (surrounding of commercial harbour)

- shipping lane
- open sea

- Application and removal
  - new build commercial vessels
  - maintenance and repair (M&R) of commercial vessels
  - removal of paint from commercial vessels.

For ship hulls, coated as 'new building' and 'maintenance & repair' application, leaching rates were calculated of 1.9 µg/cm^2/day and 1.6 µg/cm^2/day, respectively. As a conservative measure, the average leaching rate for new building, i.e. 1.9 µg/cm^2/day, was used in the PEC calculations rather than the more typical value of 1.6 µg/cm^2/day calculated for maintenance and repair.

By default an application factor of 0.9 was used in the calculations, this represents, as a worst-case scenario, the maximum market share of the active substance Cybutryne in all antifouling products. The applicant has submitted a justification stating that the estimated market share for Cybutryne amounts [redacted] of the sales for booster biocides (d'Arcy, 2005). This represents the market share of the active substance Cybutryne in all antifouling products, including [redacted] Series. The RMS considered refinement based on market share not applicable given the considerable uncertainty on future developments and the mode of action of alternative active substances.

Calculation of Predicted Environmental Concentrations (PEC)
Relevant compartments are water and sediment. It should be emphasised that suspended matter can be considered as freshly deposited sediment. Therefore in the risk assessment PEC sediment is set equal to PECsuspended matter, having the highest concentration. Additionally, it should be noticed that the calculated concentrations are average concentrations over the area of a harbour, wider environment shipping lane or open sea.

Marine compartments

In service leaching
The predicted concentrations for Cybutryne leached in service in harbour, wider environment and shipping lane and on open sea in water and sediment were:

$PEC_{inside\ harbour,\ water}$ = 63.1 ng a.s./L
$PEC_{wider\ environment\ (surrounding\ harbour),\ water}$ = 1.80 ng a.s./L

$PEC_{inside\ harbour,\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ = 1.61 ng a.s./ g dw
$PEC_{wider\ environment\ (surrounding\ harbour),\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ = 0.046 ng a.s./ g dw

$PEC_{shipping\ lane,\ water}$ = 0.054 ng a.s./L
$PEC_{shipping\ lane,\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ = 2.86E-3 ng a.s./ g dw

$PEC_{open\ sea,\ water}$ = 1.09E-3 ng a.s./L
$PEC_{open\ sea,\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ = 5.84E-5 ng a.s./ g dw

Combined emission from in service leaching, and discharge from application and removal
Harbours also having floating docks or marine lifts may have additional discharge of antifouling from application and removal. Combining these emissions will result in the following peak concentrations:

$PEC_{inside\ harbour,\ water}$ for the realistic worst-case = 420.9 ng a.s./L

$PEC_{inside\ harbour,\ water}$ for the typical case = 139.8 ng a.s./L

$PEC_{wider\ environment\ (surrounding\ harbour),\ water}$ for the realistic worst-case = 12 ng a.s./L

$PEC_{wider\ environment\ (surrounding\ harbour),\ water}$ for the typical case = 4 ng a.s./L

$PEC_{inside\ harbour,\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ for the realistic worst-case = 10.7 ng a.s./ g dw

$PEC_{inside\ harbour,\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ for the typical case = 3.6 ng a.s./ g dw

$PEC_{wider\ environment\ (surrounding\ harbour),\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ for the realistic worst-case = 0.31 ng a.s./ g dw

$PEC_{wider\ environment\ (surrounding\ harbour),\ freshly\ deposited\ sediment\ /\ suspended\ matter}$ for the typical case = 0.10 ng a.s./ g dw

PEC in sewage treatment plant (STP)

There is no requirement to calculate the PEC_{STP} for new building and maintenance and repair scenarios for commercial ships due to absence of exposure (Final minutes of TM IV 2011 and MOTA version 6).

PEC in freshwater, terrestrial and atmospheric compartments

No direct emissions to the fresh water, terrestrial and atmospheric compartments are expected from the use of Cybutryne in antifouling products for commercial coastal and ocean-going vessels. Since there is little potential for secondary exposure the predicted concentrations in freshwater, freshwater sediment, soil, groundwater and air are considered negligible.

PEC for secondary poisoning

The concentration of Cybutryne in food (fish) of fish-eating predators is calculated on basis of the maximum PEC for the marine environment, the experimentally determined BCF for whole fish and the default biomagnification factor in the predator of 1, and resulted in:

$PEC_{oral,\ predator}$: 52.6 µg a.s./kg food

2.2.2.5 Risk characterisation

Marine compartment (including sediment)

A risk characterisation for Cybutryne in the relevant aquatic compartments is shown in Table 2.2.2-3. The risk characterisation ratio is calculated as the ratio of the Predicted Environmental Concentration (PEC) to the Predicted No Effect Concentration (PNEC). When the ratio is below 1 for an environmental compartment, no adverse ecological effects are expected in that compartment.
PEC/PNEC ratios are based on $PNEC_{marine}$ of 2.0 ng/L and $PNEC_{marine\ sediment}$ of 0.04 ng/g dw. The ratios are below 1 for both the shipping-lane and open sea scenario for the in service phase. In the wider environment, however, the ratio is slightly exceeded (PEC/PNEC=1.15) and in commercial harbours the ratios for water and for freshly deposited sediment are highly exceeded.

Table 2.2.2-3 Risk characterisation for relevant aquatic compartments.

Scenario	Type of scenario	PEC_{water} (ng a.s./L)	PNEC (ng a.s./L)	PEC/PNEC	$PEC_{sediment}$ (ng a.s./g dw)	PNEC (ng a.s./g dw)	PEC/PNEC
			In service				
Commercial harbour	-	63.1	2.0	**31.6**	1.61	0.04	**40.3**
Wider environment	-	1.80	2.0	0.9	0.046	0.04	**1.15**
Shipping lane	-	0.054	2.0	0.027	2.86E-03	0.04	0.072
Open sea	-	1.09E-03	2.0	0.00055	5.84E-05	0.04	0.0015

Scenario	Type of scenario	PEC_{water} (ng a.s./L)	PNEC (ng a.s./L)	PEC/PNEC	$PEC_{sediment}$ (ng a.s./g dw)	PNEC (ng a.s./g dw)	PEC/PNEC
Application and removal (Peak conc.)							
Commercial harbour	Realistic worst-case	357.8	2.0	**179**	9.1	0.04	**228**
	Typical case	76.7	2.0	**38.3**	2.0	0.04	**48.9**
Wider environment	Realistic worst-case	10.2	2.0	**5.1**	0.26	0.04	**6.51**
	Typical case	2.2	2.0	**1.1**	0.056	0.04	**1.39**
Combined in service, application and removal (Peak conc.)							
Commercial harbour	Realistic worst-case	420.9	2.0	**210.4**	10.7	0.04	**268**
	Typical case	139.8	2.0	**69.9**	3.6	0.04	**89.2**
Wider environment	Realistic worst-case	12.0	2.0	**6.0**	0.31	0.04	**7.65**
	Typical case	4.0	2.0	**2.0**	0.10	0.04	**2.54**

According to the risk characterisation, a safe use is determined for the aquatic and sediment organisms present in a shipping lane or in open sea, whereas a risk for aquatic organisms within the commercial harbour or in the wider environment surrounding a commercial harbour cannot be excluded.

Table 2.2.2-4 Concentrations of Cybutryne in marine waters and sediments (from Cybutryne EQS dossier, 2011)

Compartment	Concentration		Reference
Marine waters (coastal and/or transitional)	< 1-36 ng/L (n=14 samples)	in surface waters in the south coast UK	Cresswell *et al*. (2006)
	< 6 – 170 ng/L	In the marina	KEMI (2006)
	< 5 – 14 ng/L	In the bay, outside the marina	
	< 4 – 42 ng/L	Natural harbour	
	< LOQ (6 – 15 ng/L)	Background location	
	< 1 – 1700 ng/L	Marinas, ports, estuaries and beaches	Konstantinou and Albanis (2004)
	95-296 ng/L	4 marinas at the German Baltic Sea coast	UBA Umweltbundesamt (2010)
Marine sediments	0.070-42 ng/g dw, median 0.46 ng/g dw	Swedish Baltic and west coasts-marinas, coastal areas and open sea background stations	Kaj et al. (2010)

A further concern, however is information derived from monitoring studies showing that cybutryne is detected in marine waters (coastal and/or transitional) at concentrations of between < 1 and 1700 ng/L and in sediments at concentrations of between 0.07 and 42 ng/g dw (median 0.46 ng/g dw) of the United Kingdom, France, Spain, Greece, the Netherlands, Switzerland, Germany, Portugal and Sweden. These monitoring concentrations exceed the PNEC for the marine and freshwater environments. Indicating that adverse effects can be expected.
Please notice that at present in many member states cybutryne is used on freshwater and marine commercial vessels and pleasure crafts, which may explain the high concentrations observed in the monitoring data. The applicant has restricted the use to commercial coastal and ocean-going vessels that remain in marine waters only.

A discussion for future development concerns adverse effects on Photosystem II (PSII) seen in algae. There are indications that PSII is an ecologically relevant indicator shown to be more sensitive than growth rate (and would lead to a lower PNEC). At present, however, there is not enough knowledge concerning this effect parameter, for consistency reasons and the late discovery of this observation in literature it was decided to leave this issue for future revision.

STP
There is no requirement to calculate the risk for the STP for new building and maintenance and repair scenarios for commercial ships due to absence of exposure (Final minutes of TM IV 2011 and MOTA version 6).

Risk mitigation measures

New building and M&R
Shipyards in the EU/EEA where ships are built, maintained and repaired are subject to both national and international regulations and codes of conduct in addition to other environmental legislation that address pollution control issues. The effect of these measures depends on both the measure itself and its efficiency, and the national authorities' enforcement of the regulations.
At TM II 2011, the results of a survey made by the Community of European Shipyards Associations (CESA, 2011) on risk mitigation measures in European shipyards were presented, together with a statement from the European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE, 2011). The goal of this work was the establishment of a list of measures applicable to each scenario and a quantified protective effect of each measure. At TM IV 2011, it was agreed that it may be considered to recommend these risk mitigation measures generally for all antifoulings, and that they can be used quantitatively if needed. These general risk mitigation measures for antifouling biocides include:

- Implementation of a specific area for paint application with hard standing (yachts)
- Shrouding: protection of the application area with plastic foils and/or fine meshed nets (yachts and commercial ships)
- Thorough cleaning of dock floor with collection of solids and wastewater (yachts and commercial ships)
- Good spraying practices: Good maintenance and control of sprayers by trained people, taking into account wind speed (professional application to yachts and commercial ships)
- Wastewater collection and pre-treatment: Oil and solids separators, settling tanks, elimination of solid wastes as dangerous wastes, … (yachts and commercial ships)
- Low emission paint removal techniques (wet blasting associated with recycling of grit (professional yachts and commercial ships).

The CEPE statement recommends using the following reduction factors for a quantitative assessment of the application risk mitigation measures:

Table 2.2.2-5 Risk mitigation measures (RMM) for paint application during commercial ship building

ESD	CESA Index (Paint spraying)	Reduction effect of the RMM (fraction of potential emission)
No measures	20	1
Dock floor discipline	15	0.75
Dock floor discipline	8.5	0.425
Use of containment (nets)		
Good spraying practices		
Dock floor discipline	7	0.35
Use of containment (nets)		
Good spraying practices		
Waste water treatment		
Dock floor discipline	5.5	0.275
Use of containment (nets)		
Good spraying practices		
Waste water treatment		
Low emission techniques		

If the emissions from typical case application activities (on a dock, compared to worst-case application on slipway) of the theoretical product whithin an OECD-EU Commercial Harbour are reduced by the factors representing dock floor discipline (0.75) and dock floor discipline, use of containment and good spraying practices (0.425), the following PEC/PNEC ratios are derived:

Table 2.2.2-6 Example of quantification of risk mitigation measures for application activities in a commercial harbour for in service and M&R in a commercial harbour for the typical case

OECD Commercial harbour scenario	Risk reduction factor	PEC/PNEC$_{harbour, water}$ [ng/L][1]	PEC/PNEC$_{harbour, freshly\ deposited\ sediment/suspended\ matter}$ [ng/g dw]
New building and M&R, application	0.75	**28.7 (38.3)**	**36.7 (48.9)**
	0.425	**16.3 (38.3)**	**20.8 (48.9)**
New building and M&R, application + in service	0.75	**52.4 (69.9)**	**66.9 (89.2)**
	0.425	**29.7 (69.9)**	**37.9 (89.2)**

1 The PEC/PNEC ratios from table 2.2.2-6 i.e. without having taken risk mitigation measures into account are given in brackets for comparison.

This example, which is calculated for illustrative purposes only, indicates that appropriate risk mitigation measures could not mitigate the identified risks for the application of Cybutryne-containing antifoulings within a commercial harbour.

Risk characterisation for the terrestrial compartment

For Cybutryne only the use on commercial deep sea and coastal vessels will be considered under the Biocidal Products Directive (BPD). The ESD considers that for this type of use professional will not result in emission to soil. Accordingly, Cybutryne residues are not considered to enter terrestrial compartments and no risk to terrestrial organisms is expected due to the lack of exposure.

Risk characterisation for the atmospheric compartment

No direct emission to air is expected from the use of Cybutryne in antifouling products for commercial coastal and ocean-going vessels. Cybutryne has a low vapour pressure (3.4×10^{-5} Pa at 25°C) and low Henry's law constant (4.1×10^{-4} Pa.m^3/mol at 20°C), so no significant volatilisation is expected. The PEC in air is therefore considered negligible. In the absence of exposure, no risk is expected.

Secondary poisoning

A simple risk characterisation for top predators (birds, mammals) exposed to Cybutryne residues *via* the food chain was performed (Table 2.2.2-7). The risk characterisation ratios (PEC/PNEC) are <1 for both representative predators. Therefore, no adverse ecological effects *via* secondary poisoning are expected from use of Cybutryne in antifouling biocidal products.

Table 2.2.2-7 Risk characterisation for top predators

Predator	PEC	PNEC	PEC/PNEC ratio
Bird	52.6 µg a.s./kg (food)	1870 µg a.s./kg (food)	0.028
Mammal		1670 µg a.s./kg (food)	0.031

2.2.3 List of endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

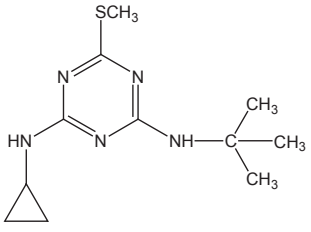
2.3 Overall conclusions

The outcome of the assessment for cybutryne in product-type 21 is specified in the BPC opinion following discussions at the meeting of 17 June 2015 of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

Appendix I: List of endpoints

Active substance (ISO Common Name)	Cybutryne
Product type	PT21 Antifouling
Applicant	Name: BASF SE. 67056 Ludwigshafen, Germany
Manufacturer of Active Substance	Name: [redacted] Address: [redacted] Ashdod [redacted]
Manufacturer of Product(s)	Name: [redacted] Address: [redacted]

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Chemical name (IUPAC)	N^2-tert-butyl-N^4-cyclopropyl-6-methylthio-1,3,5-triazine-2,4-diamine
Chemical name (CA)	*N*-cyclopropyl-*N′*-(1,1-dimethylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine
CAS No	28159-98-0
EC No	248-872-3
Other substance No.	no other numbers currently allocated
Minimum purity of the active substance as manufactured (g/kg or g/l)	975 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None
Molecular formula	$C_{11}H_{19}N_5S$
Molecular mass	257.37
Structural formula	

Physical and chemical properties

Melting point (state purity)	128.4°C (98.6%)
Boiling point (state purity)	347.3-375°C (98.6%) Cubytryne decomposes at its boiling point

Temperature of decomposition	not applicable
Appearance (state purity)	White cloddy powder (98.6%)
Relative density (state purity)	D_4^{20} = 1.11 (98.6%)
Surface tension	56.2 mN/m (98.6%) at 90% saturation
Vapour pressure (in Pa, state temperature)	3.4 * 10^{-5} Pa at 25°C
Henry's law constant (Pa m3 mol -1)	4.1 * 10^{-4} Pa *m^3* mol^{-1}
Solubility in water (g/l or mg/l, state temperature)	pH 5: 11.1 mg/L (20°C) pH 7: 9.0 mg/L (20°C) pH 9: 8.8 mg/L (20°C)
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	in hexane: 1.74 g/L at 10°C 2.04 g/L at 20°C 3.08 g/L at 30°C in methanol: 42.23 g/L at 10°C 50.58 g/L at 20°C 70.56 g/L at 30°C
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not relevant.
Partition coefficient (Log Pow) (state temperature)	pH 5: 3.2 at 10° and 25°C pH 7: 3.2 at 10° and 3.1 at 25°C pH 9: 3.2 at 10° and 3.1 at 25°C
Hydrolytic stability (DT50) (state pH and temperature) (point VII.7.6.2.1)	no hydrolysis in buffer of pH 5, 7, 9 at 50°C. No DT_{50} could be calculated.
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	pKa = 4.12
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	absorption maximum at 227 nm no significant absorption at >229 nm
Photostability (DT50) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	No DT_{50} could be derived due to slow degradation. Based on UV spectrum, photolysis is not expected to be a likely route of degradation in the environment.
Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2)	Not applicable (due to slow degradation)
Flammability	not highly flammable (98.0%) not auto-flammable (98.0%)
Explosive properties	not explosive

Classification and proposed labelling

with regard to physical/chemical data	no classification
with regard to toxicological data	Xi, R43 (according to Directive 199/45/EEC) or Skin Sens. 1, H317 (according to Regulation 1272/2008/EC)
with regard to fate and behaviour data	no classification

with regard to ecotoxicological data	N, R50/53 (according to Directive 199/45/EEC) or Aquatic Chronic 1, H410 (according to Regulation 1272/2008/EC)

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	GC-FID
Impurities in technical active substance (principle of method)	GC-FID

Analytical methods for residues

Soil (principle of method and LOQ)	Not applicable. No exposure to soil.
Air (principle of method and LOQ)	Method not required based on low vapour pressure.
Water (principle of method and LOQ)	Surface water: not required (no exposure, based on intended use of sea vessels only) Drinking water, sea water and marine sediment. Monitoring is possible based on data provided. However, the method provided is not based on a commonly available technique (further data to be provided at product authorisation).
Body fluids and tissues (principle of method and LOQ)	Not applicable. Substance is not classified as (highly) toxic.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not applicable. No residues are expected to occur based on the intended use.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Fish, shellfish (PT21 requirement). Monitoring is possible based on data provided. However, the method provided is not based on a commonly available technique (further data to be provided at product authorisation).

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	87-94% of applied dose; systemically available at least 50% (at 20/mg/kg). For risk assessment an oral absorption value of 50% will be used.
Rate and extent of dermal absorption:	5% of applied dose for human risk assessment for Cybutryne formulated as [redacted] Series based on *in vivo* rat dermal absorption study.
Distribution:	Wide distribution via blood (cellular compartment); highest tissue residues were seen in lung, heart, spleen and liver.
Potential for accumulation:	Tissue residues did not reach a plateau during 7 daily applications; due to binding of Cybutryne to blood cells, equivalents associated with tissues may rather reflect blood content of cryotomized interstitium than radioactivity associated to parenchymal tissue structures.
Rate and extent of excretion:	77-93% and 90-97% of applied dose within 48 and 168 hours after application predominantly via faeces (bile 78-79% of dose).
Toxicologically significant metabolite(s)	None

Acute toxicity

Rat LD_{50} oral	>2000 mg/k bw
Rat LD_{50} dermal	>2000 mg/k bw
Rat LC_{50} inhalation	>4090 mg/m³
Skin irritation	non-irritant
Eye irritation	non-irritant
Skin sensitization (test method used and result)	sensitizer (maximization test)

Repeated dose toxicity

Species/ target / critical effect	Rat: reduced body weight development and food consumption, increased blood cholesterol and protein, slight anaemia. Dog: reduced body weight development and food consumption, increased cholesterol, gastrointestinal irritation
Lowest relevant oral NOAEL / LOAEL	NOAEL 9.6 mg/kg bw/day (90-day rat) / LOAEL 45 mg/kg bw/day (28-day rat)
Lowest relevant dermal NOAEL / LOAEL	NOAEL 1000 mg/kg bw/day / LOAEL >1000 mg/kg bw/day (both 21-day rat)
Lowest relevant inhalation NOAEL / LOAEL	Not applicable.

Genotoxicity	No genotoxicity (5 *in vitro*, 1 *in vivo* study).

Carcinogenicity

Species/type of tumour	No data available for Cybutryne, but information based on structurally related Terbutryn: Rat (all tumours at dose level exceeding the MTD): liver adenomas (females), mammary gland adenomas and adenocarcinomas (females), thyroid gland follicular tumours (males), interstitial cell tumours in testes (males) Mice: no tumours
lowest dose with tumours	Rat: 130 mg/kg bw/day (3000 ppm) Mice: no tumours up to 3000 ppm

Reproductive toxicity

Species/ Reproduction target / critical effect	Rat: no effect on reproductive performance reduced body weight development (and food consumption), effects on kidney (P females), slight atrophy in vagina/uterus (P, F1 females in diestrus), findings in ovaries (F1 only)
Lowest relevant reproductive NOAEL / LOAEL	NOAEL 8.5 mg/kg bw/day) / LOAEL 52 mg/kg bw/day (2-generation rat study)
Species/Developmental target / critical effect	Rabbit: no teratogenic effect Dams: reduced body weight development, clinical signs Foetuses: increased post-implantation loss, reduced body weight
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	NOAEL 15 mg/kg bw/day (rabbit) / LOAEL 45 mg/kg bw/day (rabbit)

Neurotoxicity / Delayed Neurotoxicity

Species/ target/critical effect	Not applicable.
Lowest relevant developmental NOAEL / LOAEL.	Not applicable.

Other toxicological studies

...	Not applicable.

Medical data

...	No adverse health effects reported from production of active substance and formulation; no known clinical cases and poisoning incidents; no epidemiological data available one publication reports skin sensitization after application and/or removal of Cybutryne-containing antifouling paints (confirms results from animal study)

Summary	Value	Study	Safety factor
Non-professional user	Not Applicable.		
ADI (acceptable daily intake, external long-term reference dose)	Not Applicable.		
AEL (Acceptable Exposure Level)*	0.08 mg/kg bw/day	Teratogenicity study rabbits	100 (and correction of 50% oral absorption)
ARfD (acute reference dose)	Not Applicable.		

***** *In the sub-acute, semi-chronic and chronic studies in the rat there does not seem to be an effect of prolonging the exposure duration, as the NOAELs are in the same range (7.3, 9.6 and 12.2 mg/kg bw/day respectively). Therefore, the AEL is applicable for short/medium/long-term exposure.*

Acceptable exposure scenarios (including method of calculation)	
Professional users	Production of formulation [redacted] Series: low or negligible exposure expected based on qualitative assessment of production conditions (ventilation, PPE were required). Application: based on exposure data from various models or studies (in agreement with HEEG opinion endorsed at TMI 2012 and TMIV 2012) 1. Spray Painter: 51% of AEL, with gloves and double coverall (1% clothing penetration). 2. brush and rolling: 43% or 1% of AEL with gloves and impermeable coverall (5% clothing penetration). 3. Potman: 59% of AEL, with gloves and impermeable coverall (5% cloting penetration). 4. Paint stripping: 53% of AEL with gloves and impermeable coverall (5% clothing penetration). Grit filler: 103% of AEL, with gloves and impermeable coverall (5% clothing penetration).*
Production of active substance:	Not Applicable
Formulation of biocidal product	Not Applicable.
Intended uses	Mainly high pressure airless spraying, by professionals only.
Non-professional users	Not Applicable.
Indirect exposure as a result of use	Based on the environmental exposure assessment, no relevant residues are expected in matrices for human consumption (drinking water or fish/seafood; see section 3.3.6 and 3.3.8). Although not considered relevant, a reverse reference scenario showed that 269 kg of fresh fish could be eten every day for a lifetime, before filling up the ADI.

**For the exposure calculations many worst-case approaches and assumptions had to be used: dermal absorption based on in vivo rat study, worst-case assumption on the active substance present in paint to be removed, 90th percentile exposure values as 75th were not available at time when calculations were performed).*

Therefore, the slight exceeding values are considered due to the worst-case exposure calculations and therefore no adverse health effects are expected for the protected (gloves and impermeable coverall) gritt filler.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT50) (state pH and temperature)	artificial seawater, pH 8: no hydrolysis at 25°C no DT50 could be calculated.
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	sterile artificial seawater (laboratory): 7.8% degradation in 15 days, DT50 could not be determined sterile buffer, pH 7 (laboratory): 4.1% degradation in 15 days, DT50 could not be determined
Readily biodegradable (yes/no)	No
Biodegradation in seawater	no test conducted since higher tier studies are available
Non-extractable residues	not applicable
Distribution in water / sediment systems (active substance)	outdoor, seawater microcosm (800 L natural water / 5 cm layer natural sediment): treatment: ca. 560 ng a.s./L. Dissipation DT50 water: 23 days No information on NER could be established from this study
Distribution in water / sediment systems (metabolites)	outdoor, seawater microcosm (800 L natural water / 5 cm layer natural sediment): treatment: ca. 560 ng a.s./L. max. conc. [redacted] in water: 150 ng/L (28 days). Dissipation DT50 water: 23 days Metabolite [redacted] was formed in an amount of 26 % in water. No information on NER could be established from this study

Route and rate of degradation in soil

Mineralization (aerobic)	0.6% (365 days)
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT50lab (25°C, aerobic): 101 days (n = 1) DT50lab (12°C, aerobic): 285.8 days (n = 1)
	DT90lab (25°C, aerobic): not determined
	DT50lab (10°C, aerobic): no test available
	DT50lab (20°C, anaerobic): no test available
	degradation in the saturated zone: no test available
Field studies (state location, range or median with number of measurements)	DT50f: no test available
	DT90f:
Anaerobic degradation	no test available
Soil photolysis	no test available
Non-extractable residues	max. 19% of applied a.i. at day 122
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	CA 30-0155: 27.8% applied a.i. at day 122 [redacted] 14.3% applied a.i. at day 273 [redacted] 13.6% applied a.i. at day 273
Soil accumulation and plateau concentration	not determined

Adsorption/desorption

Ka , Kd	5.44 L/kg (2.59 – 7.12); n = 6
Kaoc , Kdoc	895 L/kg (472 – 1367); n = 5
pH dependence (yes / no) (if yes type of dependence)	no

Fate and behaviour in air

Direct photolysis in air	no test available
Quantum yield of direct photolysis	no test available
Photo-oxidative degradation in air	no test available
Volatilisation	vapour pressure: 3.4 × 10-5 Pa at 25°C, therefore potential for volatilisation considered to be low

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study)	no data available
Surface water (indicate location and type of study)	up to 1700 ng/L in marine water and 1.01E06 ng/kg in marine sediment
Ground water (indicate location and type of study)	no data available
Air (indicate location and type of study)	no data available

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Group / Species (habitat)	Test substance	Time-scale	Endpoint	Toxicity [µg/L]
Fish				
Menidia beryllina (marine)	a.s.	96 h, static (mm)	mortality, LC50	1,760
Oncorhynchus mykiss (freshwater)	a.s.	96 h, flow-through (n)	mortality, LC50	860
Cyprinodon variegatus (marine)	a.s.	33 d, flow-through (mm)	growth, NOEC	170
Oncorhynchus mykiss (freshwater)	a.s.	95 d, flow-through (mm)	growth, NOEC	4.0
Cyprinodon variegatus (marine)	[redacted]	96 h, static (mm)	mortality, LC50	11,000
Invertebrates				
Mysidopsis bahia (marine)	a.s.	96 h, static (n)	mortality, EC50	480
*Daphnia pulex (*freshwater)	a.s.	48 h, static (n)	mortality, EC50	5700
Mysidopsis bahia (marine)	a.s.	28 d, flow-through (mm)	reproduction, NOEC	110
Daphnia magna (freshwater)	a.s.	21 d, flow-through (mm)	reproduction, NOEC	510
Mysidopsis bahia (marine)	[redacted]	96 h, static (mm)	mortality, EC50	1,500
Algae				
Skeletonema costatum (marine)	a.s.	96 h, static (n)	growth inhibition, NOEC	0.022
Navicula pelliculosa (freshwater)	a.s.	120 h, static TWA	growth inhibition, NOEC	< 0.076
		72 h, static TWA	growth inhibition	0.02
Skeletonema costatum (marine)	[redacted]	120 h, static (mm) 72 h, static	growth inhibition, NOEC	0.18 n.d.
Navicula pelliculosa (freshwater)	[redacted]	120 h, static (mm) 72 h, static	growth inhibition, NOEC	< 77 n.d.
Aquatic plants				
Zostera marina (marine)	a.s.	10 d, semi static	photosynthetic efficiency, EC50	1.1
Ruppia maritime (marine)	a.s.	28 d	Growth EC50	0.843
Lemna gibba (freshwater)	a.s.	14 d, static	growth inhibition, NOEC	0.671
Sediment dwelling organisms				
Ampelisca abdita (marine)	a.s.	10 d (acute), spiked sediment (lm)	mortality, NOEC	44 [mg/kg dw]

Monoporeia affinis (Brackish-freshwater)	a.s.	24 h	Avoidance response (reduced burial in sediment)	0.04[mg/kg dw]
Chironomus riparius (freshwater)	a.s.	28 d, spiked water (gm)	development and emergence, NOEC	≥30.3 ≥1.2 [mg/kg dw]
Microorganisms				
Activated sludge from sewage treatment plant	a.s.	3 h, static (n)	respiration inhibition, NOEC	$>10^6$
Outdoor microcosm				
Periphyton (freshwater) - chlorophytes - Myriophyllum	a.s.	150 days, static TWA (n)	Biomass, EC10	 0.5 (10) 2 (10)
Phytoplankton;	a.s.	24 d, (n)	Bray-curtis index	2
Natural marine phyto- and zooplankton, periphyton, eelgrass, marsh grass and macro invertebrates introduced to approximately $2m^3$ systems with water collected at a natural site	a.s.	10 weeks, semi-static (3-times a week exchange of 30% of the medium + appropriate addition of the test substance) (n)	taxonomic abundance of phytoplankton, periphyton, zooplankton and macro-invertebrates; functional parameters of algae and biomass of macrophytes; NOEC	0.288-0.572
Peryphyton (marine)	a.s.	21 days,	photosynthesis	0.016

Effects on earthworms or other soil non-target organisms

Acute toxicity to …	no exposure anticipated
Reproductive toxicity to …	no exposure anticipated

Effects on soil micro-organisms

Nitrogen mineralization	no exposure anticipated
Carbon mineralization	no exposure anticipated

Effects on terrestrial vertebrates

Acute toxicity to mammals	LD50 > 2000 mg/kg bw (rat)
Acute toxicity to birds	LD50 > 2250 mg/kg bw
Dietary toxicity to birds	LC50 > 5620 mg/kg food
Reproductive toxicity to birds	no test available

Effects on honeybees

Acute oral toxicity	no exposure anticipated
Acute contact toxicity	no exposure anticipated

Effects on other beneficial arthropods	
Acute oral toxicity	no exposure anticipated
Acute contact toxicity	no exposure anticipated
Acute toxicity to …	no exposure anticipated

Bioconcentration

Bioconcentration factor (BCF)	250 L/kg (whole fish; marine species) 5200 L/kg (green macro algae)
Depuration time (DT_{50})	< 3 days, fish 9.2 days, macro algae
(DT_{90})	not determined
Level of metabolites (%) in organisms accounting for > 10 % of residues	no metabolites identified

Chapter 6: Other End Points

In vivo endocrine disruption effects	Freshwater snail *Radix balthica*: Decreased Albumen gland hypertrophy Freshwater pond snail *Lymnaea stagnalis*: NOEC for reproduction ≥ 150 µg/l (corresponding to a time weighted mean test concentration of ≥ 117 µg/l). Freshwater mud snail *Potamopyrgus antipodarum:* significant increase of total embryo numbers in all exposure groups after 4 and 8 weeks, including the lowest concentration (0.05 µg/L). The concentration-response relationship for Cybutryne resembled an inverted U.
In vitro endocrine disruption effects	

Appendix II: List of Intended Uses

Summary of intended uses

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation	Application			Applied amount per treatment			Remarks:
				Conc. of a.s.	method kind	number min max	interval between applications (min)	g as/L min max	water L/m^2 min max	m^2/L min max	
commercial deep sea and coastal vessels	The Netherlands	[redacted] series	marine algae	2.3%	predominantly by spraying	depending on service life and activity of vessels	12 months (depending on activity of vessels)	2.3	not applicable	3.5-5.8	Data were provided and accepted in support of the intended uses.

List of standard terms and abbreviations

adapted from: Guidelines and criteria for the preparation of PPP dossiers1; TNsG on Data Requirements[2])

Stand. term / Abbreviation	**Explanation**
A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADME	administration distribution metabolism and excretion
ADP	adenosine diphosphate
AE	acid equivalent
AF	assessment factor
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
Ann.	Annex
AEL	acceptable exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BAF	bioaccumulation factor
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BPD	Biocidal Products Directive
BSAF	biota-sediment accumulation factor

Stand. term / Abbreviation	**Explanation**
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degrees Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DANN
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
d	day(s)
DES	diethylstilboestrol
DIS	draft international standard *(ISO)*
DMSO	dimethylsulfoxide

1 EU (1998a): European Commission: Guidelines and criteria for the preparation of complete dossiers and of summary dossiers for the inclusion of active substances in Annex I of Directive 91/414/EC (Article 5.3 and 8,2). Document 1663/VI/94 Rev 8, 22 April 1998

2 European Chemicals Bureau, ECB (1996) Technical Guidance Documents in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances and the Commission Regulation (EC) 1488/94 for existing substances

Stand. term / Abbreviation	**Explanation**
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days post inoculation
DRP	detailed review paper *(OECD)*
$DT_{50(lab)}$	period required for 50 percent dissipation (under laboratory conditions) (define method of estimation)
$DT_{90(field)}$	period required for 90 percent dissipation (under field conditions) (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	median effective concentration
ECD	electron capture detector
ED_{50}	median effective dose
EDI	estimated daily intake
EINECS	European inventory of existing commercial substances
ELINCS	European list of notified chemical substances
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EN	European norm
EPMA	electron probe micro-analysis
ERL	extraneous residue limit
ESPE46/51	evaluation system for pesticides
EUSES	European Union system for the evaluation of substances
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FBS	full base set
FELS	fish early-life stage
FIA	fluorescence immuno-assay
FID	flame ionisation detector
F_{mol}	fractional equivalent of the metabolite´s molecular weight compared to the active substance
FOB	functional observation battery
f_{oc}	organic carbon factor (compartment dependent)

Stand. term / Abbreviation	**Explanation**
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram(s)
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPS	global positioning system
GSH	glutathione
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value)
ha	hectare(s)
Hb	haemoglobin
HC5	concentration which will be harmless to at least 95 % of the species present with a given level of confidence (usually 95 %)
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or

Stand. term / Abbreviation	**Explanation**
	high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
HUSS	human and use safety standard
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilisation concentration or median inhibitory concentration 1
ICM	integrated crop management
ID	ionisation detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
INT	2-p-iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
IUCLID	International Uniform Chemical Information Database
iv	intravenous
IVF	*in vitro* fertilisation
k *(in combination)*	kilo
k	rate constant for biodegradation
K	Kelvin
Ka	acid dissociation constant
Kb	base dissociation constant
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
kg	kilogram
K_H	Henry´s Law constant (in atmosphere per cubic metre per mole)
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
K_{ow}	octanol-water partition coefficient

Stand. term / Abbreviation	**Explanation**
Kp	solid-water partition coefficient
kPa	kilopascal(s)
l, L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
lm	lowest measured concentration
ln	natural logarithm
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
log	logarithm to the base 10
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µg	microgram
µm	micrometre (micron)
MAC	maximum allowable concentration
MAK	maximum allowable concentration
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase

Stand. term / Abbreviation	**Explanation**
mg	milligram
MHC	moisture holding capacity
MIC	minimum inhibitory concentration
min	minute(s)
MKC	minimum killing concentration
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
(mm)	mean measured concentration
MMAD	mass median aerodynamic diameter
mo	month(s)
MOE	margin of exposure
mol	mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MT	material test
MW	molecular weight
n.a.	not applicable
n-	normal (defining isomeric configuration)
n	number of observations
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometre
NMR	nuclear magnetic resonance
no, n°	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or

Stand. term / Abbreviation	**Explanation**
	detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OEL	occupational exposure limit
OH	hydroxide
OJ	Official Journal
OM	organic matter content
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
PBT	Persistent, Bioaccumulatibe, Toxic
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the acid dissociation constant
pKb	negative logarithm (to the base 10) of the base dissociation constant
PNEC	predicted no effect concentration (compartment to be added as subscript)
po	by mouth
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})

Stand. term / Abbreviation	**Explanation**
PPP	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	product type
PT(CEN)	project team CEN
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QA	quality assurance
QAU	quality assurance unit
(Q)SAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RA	risk assessment
RBC	red blood cell
REI	restricted entry interval
RENI	Registry Nomenclature Information System
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	revolutions per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
S	solubility
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SCAS	semi-continous activated sludge
SCTER	smallest chronic toxicity exposure ratio (TER)
SD	standard deviation
se	standard error

Stand. term / Abbreviation	**Explanation**
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
S/L	short term to long term ratio
SMEs	small and medium sized enterprises
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STER	smallest toxicity exposure ratio (TER)
STMR	supervised trials median residue
STP	sewage treatment plant
t	tonne(s) (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
T_{25}	tumorigenic dose that causes tumours in 25 % of the test animals
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TG	technical guideline, technical group
TGD	Technical guidance document
TID	thermionic detector, alkali flame detector
TDR	time domain reflectrometry
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit

Stand. term / Abbreviation	**Explanation**
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TNsG	technical notes for guidance
TOC	total organic carbon
Tremcard	transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TTC	2,3,5-triphenylterazoliumchloride testing method
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UR	unit risk
UV	ultraviolet
UVC	unknown or variable composition, complex reaction products

Stand. term / Abbreviation	**Explanation**
UVCB	undefined or variable composition, complex reaction products in biological material
v/v	volume ratio (volume per volume)
vis	visible
vPvB	very Persistent, very bioaccumulative
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to