Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Bijlage 3 bij RIVM-rapport 601714022 Specifieke verontreinigende en drink-water relevante stoffen onder de Kaderrichtlijn water

Selectie van potentieel relevante stoffen voor Nederland

RIVM rapport 601714022/2012

C.E. Smit | S. Wuijts

Bijlage 3 bij RIVM-rapport 601714022
Specifieke verontreinigende en drinkwater relevante stoffen onder de Kaderrichtlijn water

Selectie van potentieel relevante stoffen voor Nederland

Factsheets nieuwe stoffen

De 'factsheets' in deze bijlage zijn opgesteld in het Engels om de uitwisseling van informatie in internationaal verband te vergemakkelijken.

De volgende personen/organisaties hebben informatie aangeleverd voor deze bijlage:

André Bannink, RIWA
Rob Berbee, Waterdienst
Astrid Fischer, HWL
Caroline Moermond, RIVM
Dorien ten Hulscher, Rijkswaterstaat
Lonneke van Leeuwen, RIVM
Marcel Kotte, Waterdienst
Monique van der Aa, RIVM
Waternet
Waterschap Brabantse Delta, De Dommel, Groot Salland, Hollandse Delta, Roer en Overmaas, Reest en Wieden, Rijnland, Vallei en Eem, Velt en Vecht, Veluwe, Zuiderzeeland, Wetterskip Fryslân

Contents

Notes to the reader

Status of the information

The factsheets in this appendix present background information on compounds that were put forward by stakeholders as candidates for the new 'Dutch watchlist'. This list contains (new) substances for which monitoring data indicate that they might become a problem for the ecological and/or drinking water function of Dutch surface waters, but for which too little information is available at this stage for standard setting and/or inclusion in national legislation under the Water Framework Directive (WFD).
The Dutch watchlist has no legal status, but is meant to focus further research, e.g. concerning monitoring or (eco)toxicological risks. The factsheets should therefore be considered as a 'screening tool', and not as definitive substance evaluations. The information has been retrieved from various sources (e.g. databases, internet sources, evaluations from other countries), but underlying data have not been checked. This means that the information should be considered as indicative only. This especially holds for the risk limits that are presented. Unless otherwise stated, they do not have an official status and should therefore not be used as official water quality standards.

Information on removal upon water treatment

The WFD requires that surface water quality should be sufficient for drinking water production, without increasing the current efforts for purification. Instead, the level of purification should be as low as possible. In view of this, one of the aspects considered by the Association of River Waterworks (RIWA) for putting forward potentially relevant compounds is the fact whether or not a compound is expected to be removed by simple water treatment. The main chemical properties that influence the removal by water treatment are polarity, volatility and biodegradation (relevant for removal by powdered activated carbon). The log K_{ow} and vapour pressure (VP in mm Hg at 20 °C) have been used as a measure for polarity and volatility, respectively. As a measure for biodegradability, the primary biodegradation model BioWIN3 is used, that is included in EPISuite [1].

Derivation of risk limits

When established or proposed environmental risk limits (ERLs) were not available from other sources, values are presented that are based on (eco)toxicological information, following as much as possible the methodology that would be applied for derivation of water quality standards under the WFD.

Criteria used for further actions

Each factsheet ends with a summary and discussion, followed by conclusions and recommendations. In the summary and discussion, the available information is weighed and risk ratios are presented with respect to ecology and drinking water function. The criteria have been applied to conclude on further actions and recommendations, which are described in section 4.3 of the main report.

List of terms and abbreviations used in the factsheets

AA-EQS	Environmental Quality Standard based on Annual Average concentrations
ADI	Acceptable Daily Intake
AEL	Acceptable Exposure Level
BCF	Bioconcentration Factor
BKMW	Besluit kwaliteitseisen en monitoring water, Dutch decree on water quality and monitoring in the context of the WFD
CBG	College ter Beoordeling van Geneesmiddelen, Dutch Medicines Evaluation Board
Ctgb	College ter beoordeling van gewasbeschermingsmiddelen en biociden, Dutch board for the authorisation of plant protection products and biocides
DMR-memorandum	Danube, Meuse and Rhine memorandum, containing target values for drinking water abstraction
DNEL	Derived No Effect Level
DT_{50}	halflife time for degradation
ECHA	European Chemicals Agency
EC_x	concentration at which x% effect is observed
EMEA	European Medicines Agency
EPA	Environmental Protection Agency
EQS	Environmental Quality Standard for water under the WFD
ERL	Environmental Risk Limit
ESIS	European chemical Substances Information System
EU-RAR	European Union Risk Assessment Report, prepared within the context of the former existing substances regulation
GIP	Genees- en hulpmiddelen Informatie Project
HWL	Het Waterlaboratorium
ICPR / ICBR	International Commision for the Protection of the Rhine / Internationale Commissie ter Bescherming van de Rijn
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{oc}	organic carbon partitioning coefficient
K_{ow}	octanol water partition coefficient
KRW	Kaderrichtlijn water, translation of WFD
LC_{50}	lethal concentration for 50% of the test species
LOEL	Lowest Observed Effect Level
LOQ	Limit of Quantification
MAC-EQS	Maximum Acceptable Concentration Environmental Quality Standard, referring to short term peak exposure
MKN	Milieukwaliteitsnorm, Dutch quality standard for surface water (translation of EQS)
MPC	Maximum Permissible Concentration, risk limit for long term exposure
MSDS	Materials Safety Datasheet
NO(A)EC	No Observed (Adverse) Effect Concentration
NO(A)EL	No Observed (Adverse) Effect Level
OECD	Organization for Economic Cooperation and Development
PBT	Persistent Bioaccumulative Toxic
PET	Polyethylene terephthalate
PNEC	Predicted No Effect Concentration
$PNEC_{oral}$	Predicted No Effect Concentration for predators, expressed as a concentration in feed
POCIS	Polar Organic Chemical Integrative Samplers
POP	Persistent Organic Pollutant
PRTR	Pollutant Release and Transfer Register
Pt	Product type for biocidal products
QS	Quality Standard

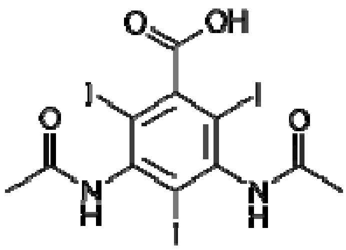
QSAR	Quantitative Structure Activity Relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIWA	Vereniging van Rivierwaterbedrijven / Association of River Waterworks
RIZA	Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
TDI	Tolerable Daily Intake
TL_{hh}	human toxicological threshold limit (TDI, ADI etc.)
VP	vapour pressure
Waterdienst	Centre for Water management of the Dutch Ministry of Infrastructure and Environment
WFD	Water Framework Directive (2000/60/EC)
WHO	World Health Organization
WQK	Wasser Qualitäts Kritrium, German water quality criterion
WQZ	Wasser Qualitätsziel, German water quality objective

1 Amidotrizoic acid

1.1 Introduction

Amidotrizoic acid (also known as diatrizoic acid) is put forward by the RIWA as a drinking water relevant compound because it is frequently present in surface water used for drinking water abstraction and almost impossible to remove by simple water treatment. Furthermore, as a pharmaceutical product it may give rise to public concern, and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies. The compound is included in the monitoring program ('Rijnstoffenlijst 2011') of the International Commission for the Protection of the Rhine [2] because of its relevance for drinking water production.

1.2 Chemical identity

Name	Amidotrizoic acid, diatrizoic acid
Chemical name	3,5-diacetamido-2,4,6-triiodobenzoic acid
CAS number	117-96-4 (acid); 737-31-5 (Na-salt); 131-49-7 (Meglumine salt)
EC number	204-223-6
Molecular formula	$C_{11}H_9I_3N_2O_4$
Molar mass	613.91
Structural formula	
SMILES code	CC(=O)Nc1c(I)c(NC(C)=O)c(I)c(C(O)=O)c1I

1.3 Information on uses and emissions

Amidotrizoic acid is registered as a human pharmaceutical in the Netherlands. Amidotrizoic acid is used as a radio contrast fluid. It enters Dutch waters from local use, but also in rivers (like the Rhine), resulting from use in upstream countries. In 2001, 60,686 kg was sold in Germany and Switzerland [3]. Two products are registered in the Netherlands [4]. Data on use in the Netherlands are not available, the compound is included in the GIP-database [5], but only one user is indicated for 2009. Emission data are not available, the compound is not included in the Pollutant Release and Transfer Register [6].

1.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human pharmaceutical in NL

1.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
DE	≤ 0.1 – 1.0	drinking water standard for iodin-containing contrast fluids	[3]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

1.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification		not included in ESIS or C&L inventory	[8,9]
log K_{ow}	1.4	estimated acid; EpiSuite	[1,10]
Bioconcentration factor (BCF)	3.16	estimated; EpiSuite	[1]
Human toxicological threshold limit (TL_{hh})	5000 mg/person	provisional	[11]

1.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2001-2008	0.01	0.61	0.208		Lobith	RIWA in [3]
	0.01	0.39	0.09		Andijk	RIWA in [3]
	0.01	0.84	0.202		Nieuwegein	RIWA in [3]
	0.01	1.2	0.194		Nieuwersluis	RIWA in [3]
	0.01	0.083			Tapwater	Mons et al., 2003 in RIWA in [3]
2006	<	<	<		1 (Brakel)	[12]
	0.05	0.35	0.182	0.341	12 (Lobith)	
	0.093	0.26	0.156	0.248	13 (Nieuwegein)	
	0.074	0.34	0.147	0.284	13 (Nieuwersluis)	
	0.03	0.14	0.0785	0.124	13 (Andijk)	
2007	0.032	0.097	0.0628		4 (Brakel)	[12]
	0.11	0.41	0.191	0.407	12 (Lobith)	
	0.02	0.53	0.165	0.498	13 (Nieuwegein)	
	0.028	0.33	0.119	0.278	13 (Nieuwersluis)	
	<	0.22	0.0665	0.192	13 (Andijk)	
2008	<	0.073	<		4 (Heel)	[12]
	0.072	0.45	0.207		4 (Brakel)	
	<	0.11	0.0587		9 (Keizersveer)	
	0.14	0.61	0.265	0.57	13 (Lobith)	
	0.097	0.84	0.341	0.764	13 (Nieuwegein)	
	0.15	1.2	0.355	0.944	13 (Nieuwersluis)	
	0.057	0.39	0.161	0.33	13 (Andijk)	
2009	<	0.23	0.0672		4 (Brakel)	[12]
	<	0.43	0.0902	0.39	11 (Keizersveer)	
	0.13	0.47	0.262	0.438	13 (Lobith)	
	<	0.47	0.121	0.422	13 (Nieuwegein	

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
	0.19	0.62	0.328		4 (Nieuwersluis)	
	<	0.32	0.0702	0.296	13 (Andijk)	
2010	0.05	0.19	0.105	0.178	13 (Brakel)	[12]
	0.07	0.37	0.15	0.33	13 (Keizersveer)	
	0.099	0.22	0.172	0.217	12 (Lobith)	
	0.05	0.24	0.126	0.219	12 (Nieuwegein)	
	0.05	0.17	0.129	0.166	13 (Nieuwersluis)	
	0.03	0.16	0.0913	0.156	13 (Andijk)	
	0.05	0.18	0.125	0.174	12 (Stellendam)	

There is a tendency towards decreasing concentrations as from 2009. The average of the 90^{th} percentile concentrations in 2010 is 0.21 µg/L.

The Water board Roer and Overmaas provided monitoring data for one location in the River Roer in April, August and October 2009, concentrations ranged from 0.58 to 1.3 µg/L, which is higher than measured by the RIWA.

1.8 Removal upon water treatment

Based on a log K_{ow} of 1.37, VP of 3.57E-15 and BIOWIN3 value of 1.6871 (months to recalcitrant), amidotrizoic acid is considered very difficult to remove by simple surface water treatment (only 0-40% removed). Radiocontrast agents are in general hardly removed by current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

1.9 Environmental risk limits based on direct ecotoxicity

No regulatory standard or reliable proposal is available.
According to the ICBR report, no toxicity data for amidotrizoic acid are available. No ecotoxicological data could be found in databases or on the internet. QSAR-estimates with the program ECOSAR (included in EpiSuite, [1]) indicate that the compound is relatively non-toxic, with acute L/EC_{50} values in the g/L range, and chronic endpoints in the mg/L range. Based on the criteria to use QSARs for derivation of indicative Maximum Permissible Concentrations in the Netherlands (MPCs; [13]), the L/C_{50}-value for fish (2510 mg/L) would be acceptable.

1.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

1.11 Environmental risk limits based on human toxicology

1.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 5000 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (5000 x 0.1) / 2 = 250 mg/L.

The proposed target value for pharmaceuticals according to the Danube, Meuse and Rhine (DMR)-memorandum [7] and ICBR [3] is 0.1 µg/L.

1.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

1.12 Summary and discussion

No data are available on the ecotoxicity of amidotrizoic acid, QSAR-values suggest that the compound is relatively non-toxic to aquatic organisms, but only the value for fish would be accepted for an indicative MPC. There are no toxicological data, and the provisional drinking water limit has been derived from the lowest effective dose. This results in a value of 250 mg/L, which is much higher than the target value as proposed by the drinking water companies of 0.1 µg/L. The monitoring dataset is quite extensive, showing a consistent pattern with 90th percentile concentrations of around 0.2 µg/L in 2010 at multiple locations. It is noted that concentrations in smaller water bodies may be higher, as indicated by monitoring data from the River Roer. Based on the target value of 0.1 µg/L as proposed in the DMR-memorandum and the overall average of 90th percentile concentrations in 2010 of 0.21 µg/L, the risk ratio is 2. Using the drinking water limit based on human-toxicological data, the risk ratio is 8.4×10^{-5}.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	?	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	250,000	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.21	µg/L
Risk ratio	2	ERL DMR
	<0.0001	ERL DW
	?	ERL ECO

n.r. = not relevant

1.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90th percentile concentrations exceed the DMR-target value on various locations and occasions, but are much lower than the risk limit based on human toxicology;
- relevance for ecology unknown, because ecotoxicity data are not available.

Recommendations

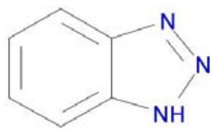
- continue monitoring;
- establish relevance for ecology.

2 Benzotriazole

2.1 Introduction

Benzotriazole has been put forward by the Waterdienst because of its widesprad use as anti-corrosive in cooling towers. As a result, emissions to surface water are expected. The RIWA considered benzotriazole as a drinking water relevant compound, because it is an emerging substance that is frequently present in surface water used for drinking water abstraction.

2.2 Chemical identity

Name	benzotriazole
Chemical name	1H-Benzotriazole, 1,2,3-Benzotriazole
CAS number	95-14-7
EC number	202-394-1
Molecular formula	C6H5N3
Molar mass	119.12
Structural formula	
SMILES code	c1ccc2nnnc2c1

2.3 Information on uses and emissions

Benzotriazole is a complexing agent and as such is a useful corrosion inhibitor. The main use in the Netherlands is in recirculating cooling systems in which copper is used in the heat exchangers. It is also used for silver protection in dishwashing detergents and as an anti-fog agent in photographic development. Aircraft de-icer and anti-icer fluid also contain benzotriazole. The compound is not included in the Pollutant Release and Transfer Register [6].

2.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	D: Classified as water hazardous class 1 [14]

2.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
CH	30	AA-EQS for direct ecotoxicity, No Observed Effect Concentration (NOEC) *Daphnia magna* with AF 100	[15]
CH	120	MAC-EQS, EC_{50} *Oncorhynchus mykiss* with AF 100	[15]
	1	target value for anthropogenic compounds in surface water for abstraction of drinking water	[7]

2.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	R20/22, R36, R52/53	materials safety datasheet (MSDS)	[16]
	H302, 318, 319, 332, 412, 413	notified classification	[8]
log K_{ow}	1.44	experimental EpiSuite	[1]
BCF	3.34	estimated log K_{ow} 1.44	[17]
Human toxicological threshold limit (TL_{hh})	0.295 mg/kg bw.d		[10]

2.7 Environmental concentrations

2.7.1 Netherlands

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
2007	0.097	0.54	0.24	0.306	0.537	12 (Lobith)	[12]
2008	0.041	1.1	0.23	0.309	0.86	13 (Lobith)	
2009	0.15	0.97	0.3	0.363	0.794	13 (Lobith)	
2010	0.29	0.81	0.425	0.47	0.747	12 (Lobith)	

2.7.2 Information from other countries

In a EU-wide survey, polar organic pollutants were analysed in unfiltered water samples collected in 2007 at 122 sampling stations in streams and rivers in 27 European countries [18]. Benzotriazole was detected in 94% of the samples (reporting limit 1 ng/L). The maximum level was 1.4 µg/L. The average and median were 0.49 and 0.23 µg/L, respectively, the 90^{th} percentile was 1.2 µg/L.

2.8 Removal upon water treatment

Based on a log K_{ow} of 1.44, VP of 2.46E-45 and BIOWIN3 value of 2.9359 (weeks to months), benzotriazole is considered difficult to remove by the current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

2.9 Environmental risk limits based on direct ecotoxicity

For the present assessment, a chronic ERL of 30 µg/L is selected (see section 2.5).

2.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

2.11 Environmental risk limits based on human toxicology

2.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.295 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.295 x 0.1 x 70) / 2 = 1.0 mg/L = 1000 µg/L.

For anthropogenic organic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

2.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

2.12 Summary and discussion

The lowest chronic risk limit is 30 µg/L, based on direct ecotoxicity. The quality of this risk limit is good, since it is based on a thorough literature survey performed by known experts. The monitoring dataset is restricted to one location. From the data from 2007 to 2010 there appears to be a trend to increasing concentrations with time, although maximum levels in 2010 are slightly lower than in 2009. The compound has been detected all over Europe. The 90th percentile concentration for 2010 of 0.747 µg/L is lower than the DMR-target value, and the ratio between measured concentrations and the risk limit based on human toxicological information is <0.001. Using the chronic ERL of 30 µg/L for direct ecotoxicity, the risk ratio is 0.02. The ratio between the observed maximum concentration in 2010 of 0.81 µg/L and the MAC-EQS of 120 µg/L is 0.007. If concentrations increase again, the compound might exceed the target value of 1 µg/L, and the risk ratio with respect to ecology might increase.

ERL DMR-memorandum	1	µg/L
ERL direct ecotoxicity	30	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	1000	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.747	µg/L
Risk ratio	0.75	ERL DMR
	<0.001	ERL DW
	0.02	ERL ECO

n.r. = not relevant

2.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90th percentile concentrations do not exceed the DMR-target value, it is only monitored at one location (Lobith) so wider occurrence is unknown; risk limit based on human toxicology >> DMR-value;
- potentially relevant for ecology, because the risk ratio is > 0.01.

Recommendation

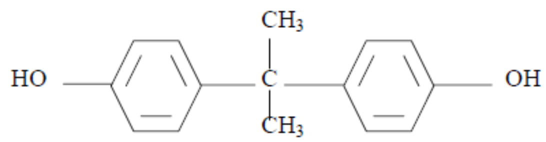
- continue monitoring and expand to other locations.

3 Bisphenol A

3.1 Introduction

Bisphenol A (BPA) has been put forward by the RIWA as a drinking water relevant compound, because it is considered toxicologically relevant and frequently present in surface water used for drinking water abstraction. The compound is a suspected endocrine disrupter and is included in the list of candidate substances for the monitoring program for 2014 of the International Commission for the Protection of the Rhine [2].

3.2 Chemical identity

Name	Bisphenol A
Chemical name	2,2-bis(4-hydroxyphenyl)propane
CAS number	80-05-7
EC number	201-245-8
Molecular formula	$C_{15}H_{16}O_2$
Molar mass	228.29
Structural formula	
SMILES code	C(C)(C)(c1ccc(O)cc1)c2ccc(O)cc2

3.3 Information on uses and emissions

BPA is an organic compound with two phenol functional groups. It is used to make polycarbonate plastic and epoxy resins, along with other applications. BPA is also a precursor to the flame retardant tetrabromobisphenol A, and was formerly used as a fungicide. BPA is a preferred colour developer in carbonless copy paper and thermal paper. BPA-based products are also used in foundry castings and for lining water pipes. According to the EU Risk Assessment Report (EU-RAR), total estimated use in the EU was 685,000 tonnes/year, based on figures over 1996-1999 [19]. In the Netherlands, BPA is produced at two locations (Bergen op Zoom and Pernis). Emissions occur from leaching of BPA from plastic. In the European Union and Canada, BPA use is banned in baby bottles as from 2011. The safety of the use of BPA in medical devices is subject of an investigation by the Scientific Committee on Emerging and newly Identified Health Risks [20]. The compound is not included in the Pollutant Release and Transfer Register [6].

3.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Included
Existing Substances Reg. (793/93/EC)	EU-RAR report available [19]
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	D: Classified as water hazardous class 2 [14]

3.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
	1.5	Predicted No Effect Concentration (PNEC), SSD on chronic data with AF 5	[19]
	18	PNEC REACH dossier	[8]
	0.1	target value for endocrine disrupting compounds in surface water for abstraction of drinking water	[7]

3.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H317, 318, 335, 361	harmonised classification	[8]
BCF	67 L/kg 144 L/kg	fish clams	[19]
Human toxicological threshold limit (TL_{hh})	50 µg/kg bw.d		[21]
Endocrine disrupter	Inconclusive, but considered to be covered in the EU-RAR		[19]

3.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	95^{th} percentile [µg/L]	Remark	Reference
1999	<0.011	0.17	<0.018		0.16	detected in 2 out of 7 samples; Dommel, Meuse, Bergermeer	[19]
	<0.088	1.0	0.018		0.322	detected in 50 out of 97 samples nationwide	
1997	0.0099	0.16	0.0355		0.108	detected in 10 out of 12 samples; large rivers and Noordzeekanaal	[19]
2006	*	*	*	*	*	1 (Lobith)	[12]
	0.008	0.044	0.016	0.020	0.043	13 (Nieuwegein)	
	0.016	0.047	0.026	0.029	0.045	13 (Nieuwersluis)	
2007		0.023				single value Nieuwegein	[22]
2007	0.014	0.160	0.025	0.046	0.135	13 (Nieuwegein)	[12]
	<	<	<	<	<	50 (Heel)	
2008	<	0.07	*	<	*	4 (Luik)	[12]
	<	1.5	<	<	<	147 (Heel)	
2009	<	<	<	<	<	123 (Heel)	[12]
2010	<	<	*	<	*	4 (Namêche)	[12]
	<	0.14	*	0.046	*	4 (Luik)	
	<	<	<	<	<	53 (Heel)	

* quantification not reliable, reporting limit 0.5 µg/L

The measured concentrations are indicative values, since the reporting limit is higher (0.5 µg/L).

BPA is not found in industrial discharges, or concentrations are below the reporting limit (Rob Berbee, pers. comm.). Measured concentrations in STP-effluents are 0.13 µg/L (average), 0.19 µg/L (90^{th} percentile), maximum is 1.7 µg/L (Waterdienst data).

3.8 Removal upon water treatment

Based on a log K_{ow} of 3.64, VP of 2.27E-07 and BIOWIN3 value of 2.5953 (weeks to months), BPA is considered difficult to remove by simple surface water treatment. In practice, however, this is not the case as BPA is removed for 80-100% by coagulation. However, there is no guarantee that all BPA will be removed and because of its endocrine disrupting properties the compound is still considered relevant.

3.9 Environmental risk limits based on direct ecotoxicity

For the present assessment, the PNEC of 1.5 µg/L from the EU-RAR [19] is selected.

3.10 Environmental risk limits based on secondary poisoning

Secondary poisoning is relevant in view of the BCF. In the EU-RAR [19], the $PNEC_{oral}$ for secondary poisoning is based on a No Observed Adverse Effect Level (NOAEL) of 10 mg/kg bw per day for chickens. A factor of 8 is applied to convert the daily dose into a concentration in feed, giving a No Observed Effect Concentration (NOEC) of 80 mg/kg; applying an assessment factor of 30 gives a $PNEC_{oral}$ of 2.67 mg/kg food.
Based on the $PNEC_{oral}$ of 2.76 mg/kg food and a BCF of 144 L/kg for clams, the ERL for secondary poisoning is 2.76 / 144 = 0.019 mg/L = 19 µg/L.

3.11 Environmental risk limits based on human toxicology

3.11.1 Surface water for drinking water abstraction

Input: TL_{hh}= 50 µg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (50 x 0.1 x 70) / 2 = 175 µg/L.

According to the DMR-memorandum, a target value of 0.1 µg/L would apply in view of suspected endocrine disrupting properties.

3.11.2 Surface water for fish consumption

Human fish consumption is relevant in view of the BCF in combination with reproductive effects.
Input: TL_{hh} = 50 µg/kg bw.d, 115 g fish/shellfish per day, body weight 70 kg;, 10% of TL_{hh} allowed via fish consumption, BCF = 144 L/kg.
ERL (food) = (50 x 0.1 x 70) / 0.115 = 3043 µg/kg fish
ERL (water) = 3043 / 144 = 21 µg/L.

3.12 Summary and discussion

Bisphenol-A is a suspected endocrine disrupter, which is the main reason for restrictions on the use in consumer products. This is also the reason for the drinking water companies to promote a target value of 0.1 µg/L for surface water used for drinking water production. The ecotoxicological data have been evaluated on the European level, and the PNEC is considered to be reliable. The monitoring data are restricted to a few locations only, and analytical methods appear to be not reliable. The monitoring data of the RIWA indicate that the compound is not often detected above the limit of quantification of 0.5 µg/L. This LOQ is, however, higher than the target value as proposed in the DMR-memorandum, and close to the PNEC for water. A 90^{th} or 95^{th} percentile is not available, the average concentration is 0.05 µg/L. The compound is also detected in effluents of sewage treatment plants (STP), 90^{th} percentile concentration is 0.19 µg/L. Assuming a 10-fold dilution factor, the estimated concentration in surface water would be 0.02 µg/L. This is in accordance with measured data.
Based on the average concentration of 0.05 µg/L, and the ERL of 1.5 µg/L for direct ecotoxicity, the risk ratio is 0.03. Using the target value of 0.1 µg/L as proposed in the DMR-memorandum, the risk ratio is 0.5. Based on the ERL for drinking water based on human toxicology, the risk ratio is <0.001.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	1.5	µg/L
ERL secondary poisoning	19	µg/L
ERL drinking water	175	µg/L
ERL human fish consumption	21	µg/L
Environmental concentration	0.05	µg/L
Risk ratio	0.5	ERL DMR
	<0.001	ERL DW
	0.03	ERL ECO

3.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- monitoring data are limited to a few locations and quantification is not reliable; 90th percentile concentrations do not exceed the DMR-target value and are much lower than the risk limit based on human toxicology;
- potentially relevant for ecology, because the risk ratio is > 0.01.

Recommendation

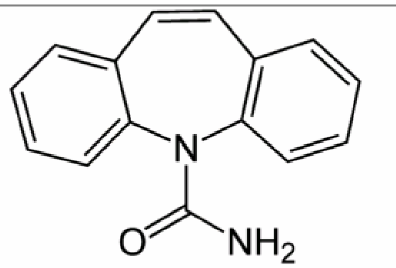
- continue monitoring and improve analysis.

4 Carbamazepine

4.1 Introduction

Carbamazepine has been put forward by the RIWA as a drinking water relevant compound because it is considered toxicological relevant and frequently present in surface water used for drinking water abstraction. Furthermore, medicinal products are considered as substance that may rise public concern. The risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies. The Waterdienst also put forward carbamazepine as a potential relevant compound, because together with its degradation product iminostilbene it is one of the drugs that is most frequently found in surface water. The compound has been considered for the list of priority substances under the WFD, and is included in the monitoring program ('Rijnstoffenlijst 2011') of the International Commission for the Protection of the Rhine [2] because of its relevance for drinking water production.

4.2 Chemical identity

Name	Carbamazepine
Chemical name	5*H*-Dibenz[b,f]azepine-5-carbamide
CAS number	298-46-4
EC number	206-062-7
Molecular formula	$C_{15}H_{12}N_2O$
Molar mass	236.27
Structural formula	
SMILES code	NC(=O)N1C2=C(C=CC=C2)C=CC2=C1C=CC=C2

4.3 Information on uses and emissions

Carbamazepine is an active pharmaceutical ingredient used for the treatment of epilepsy, trigeminal neuralgia, bipolar depression, excited psychosis, and mania. A total of 36 products are registered in the Netherlands [4]. The estimated number of users in the Netherlands shows a decreasing from almost 56,000 in 2006 to around 47,000 in 2010 [5]. The estimated total use was 8400 kg in 2007, and is expected to increase to 8990 kg by 2020 [23]. The estimated emission in the Netherlands to surface water and STP increased from 1046 kg/y in 1999 to 1107 kg/y in 2000. Estimated emissions to surface water were 1090, 1093 and 1067 kg/y in 2005, 2007 and 2008, respectively [6].

4.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	D: Classified as water hazardous class 2 [14]

4.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
CH	0.5	AA-EQS, NOEC *Ceriodaphnia dubia*, with AF 50	[24]
CH	2550	MAC-EQS, EC_{50} *Lemna minor* with AF 100	[24]
F	2.5	EQS, NOEC *Ceriodaphnia dubia* with AF 10	[25]
EU	0.5	draft AA-EQS, NOEC *Ceriodaphnia dubia* with AF 50	[26]
	4.92	PNEC	[27]
	17	PNEC, industry materials safety datasheet (MSDS), NOEC fish with AF 1000	[28]
	170	indicative PNEC, industry MSDS, NOEC fish with AF 100	[29]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

4.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 317, 304, 334, 351, 360, 361, 410, 412	notified classification	[8]
BCF	61-63 L/kg	estimated	[26]
Human toxicological threshold limit (TL_{hh})	15.9 µg/kg bw.d		[26] (Cunningham et al., 2010)
	1 mg/person	provisional value	[11]
	0.34 µg/kg bw.d		[10]

4.7 Environmental concentrations

4.7.1 Netherlands

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark n (location)	Reference
2003		0.227				263 measurements; RIWA data	[10]
2006	<	0.12	0.06	0.0539	0.081	28 (Brakel)	[12]
	0.03	0.12	0.065	0.0692	0.12	12 (Lobith)	
	0.04	0.15	0.08	0.0821	0.112	117 (Nieuwegein)	
	0.05	0.13	0.09	0.0893	0.118	15 (Nieuwersluis)	
	<	0.08	0.07	0.0635	0.08	13 (Andijk)	
2007	<	0.07	0.05	<	0.06	29 (Brakel)	[12]
	0.027	0.14	0.06	0.0716	0.136	13 (Lobith)	
	<	0.12	0.08	0.067	0.11	13 (Nieuwegein)	
	0.05	0.1	0.08	0.0757	0.095	14 (Nieuwersluis)	
	0.04	0.07	0.05	0.05	0.07	13 (Andijk)	
2008	<	0.06	*	<	*	8 (Luik)	[12]
	<	0.07	<	<	0.062	27 (Brakel)	
	<	0.09	<	<	0.086	13 (Keizersveer)	
	0.026	0.12	0.057	0.061	0.109	13 (Lobith)	
	0.05	0.08	0.07	0.0669	0.08	13 (Nieuwegein)	
	0.05	0.11	0.08	0.08	0.106	13 (Nieuwersluis)	
	0.04	0.06	0.05	0.05	0.06	13 (Andijk)	
2009	0.059	*	0.03	*	*	7 (Luik)	[12]
	<	<	<	<	<	122 (Heel)	
	<	0.13	0.06	0.059	0.11	29 (Brakel)	
	0.03	0.12	0.06	0.0687	0.12	15 (Keizersveer)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark n (location)	Reference
	0.039	0.16	0.078	0.0824	0.144	13 (Lobith)	
	<	0.08	0.06	0.0565	0.076	13 (Nieuwegein)	
	0.07	0.12	0.08	0.0831	0.112	13 (Nieuwersluis)	
	<	0.07	0.05	0.0481	0.066	13 (Andijk)	
2009		0.61		0.21		16 occasions during screening	[30]
2010	<	0.07	0.014	0.0189	0.0654	10 (Namêche)	[12]
	<	0.057	0.016	0.0193	0.0539	10 (Luik)	
	<	<	<	<	<	53 (Heel)	
	<	0.1	0.055	0.0513	0.083	26 (Brakel)	
	0.02	0.1	0.06	0.0562	0.096	13 (Keizersveer)	
	0.033	0.11	0.0475	0.0565	0.102	12 (Lobith)	
	<	0.1	0.065	0.0679	0.1	12 (Nieuwegein)	
	<	0.11	0.08	0.0754	0.106	13 (Nieuwersluis)	
	<	0.14	<	0.055	0.128	13 (Andijk)	
	0.04	0.06	0.05	0.0508	0.06	12 (Stellendam)	

The overall average of 90^{th} percentile values of Dutch sampling stations of the RIWA over 2010 is 0.1 µg/L. The average concentration of 0.21 µg/L found during screening monitoring by the Waterdienst in 2010 is higher than the concentrations measured by the RIWA. This is also the case for the average and 90^{th} percentile values of 0.13 and 0.24 µg/L found during screening monitoring by the Water board Brabantse Delta.

During screening monitoring in 2003, the Water board De Dommel found concentrations of carbamazepine between 0.02 and 0.53 µg/L. In 2008, concentrations at nine locations in the Dommel area ranged from 0.05 to 0.62 µg/L.

Water board Roer and Overmaas (Province of Limburg) provided monitoring data for five locations in 2009, one of which is located at the German border near Brunssum. Results are summarised below.

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark n (location)
2009	0.28	0.64		0.41	0.57	4 (Anselderbeek)
2009	0.34	0.77		0.57		3 (Wolfhagermühle)
2009	0.12	0.42		0.21	0.30	13 (Roer)
2009	0.47	0.73		0.62	0.72	4 (Worm, Haanrade)
2009	0.51	0.73		0.67	0.73	4 (Worm, Mariënberg)

Water board Brabantse Delta (Province of North-Brabant) provided data for 12 locations that were sampled in May and June, 2011. Concentrations ranged from below the reporting limit to 0.45 µg/L.

Rademaker and De Lange [31] presented a summary of monitoring data of pharmaceuticals in the Netherlands, based on an unpublished study [32], RIWA reports from 2003, 2004 and 2005 and a RIZA report from 2003 [33]. Carbamazepine was found in 99 out of 153 samples (65%), the highest concentration was 0.26 µg/L, the average was 0.067 µg/L.

In a research project with passive samplers, carbamazepine was detected on several locations. Based on the residues in POCIS samplers, estimated concentrations in water ranged from 0.8 to 9.5 ng/L [34]. This is higher than the concentrations reported by the RIWA, which may be due to methodological differences.

Concentrations in STP-effluents are 0.18–1.6 μg/L, 90th percentile 1.06 μg/L (Waterdienst data). In 2010, Water board Rijnland measured concentrations in an STP-influent between 0.23 and 0.7 μg/L, the 90th percentile was 0.61 μg/L. Concentrations in STP-effluent ranged from 0.19 to 0.65, the 90th percentile was 0.61 μg/L.

4.7.2 *Information from other countries*

Country	Year	Value [μg/L]		Reference
D	2008	0.59	maximum of average by station (n = 94)	[26]
	2008	1.2	maximum of analyses	[26]
N		1.0	estimated from sales data	[27]
S		1.1	estimated from sales data	[27]

4.8 Removal upon water treatment

Based on a log K_{ow} of 2.45 VP of 1.84E-07 and BIOWIN3 value of 2.6770 (weeks to months), carbamazepine is considered difficult to remove by current methods for surface water treatment (only 0-40% removed). Reduction of the level of purification treatment will not be possible.

4.9 Environmental risk limits based on direct ecotoxicity

For the present assessment, the chronic AA-EQS of 0.5 μg/L is selected as ERL.

4.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

4.11 Environmental risk limits based on human toxicology

4.11.1 *Surface water for drinking water abstraction*

Input: TL_{hh} 15.9 μg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (15.9 x 0.1 x 70) / 2 = 56 μg/L

Input: TL_{hh} = 1 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (1 x 0.1) / 2 = 0.05 mg/L = 50 μg/L.

Input: TL_{hh} = 0.34 μg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.34 x 0.1 x 70) / 2 = 1 μg/L

Depending on the human toxicological data, drinking water limits between 1 and 56 μg/L are derived. These values are all higher than the ecotoxicological risk limit of 0.5 μg/L and the proposed target value of 0.1 μg/L for pharmaceuticals according to the DMR-memorandum.

4.11.2 *Surface water for fish consumption*

Considered relevant in view of reproductive effects in mammalian studies.

Input: TL_{hh} = 15.9 μg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 63 L/kg.
ERL (food) = (15.9 x 0.1 x 70) / 0.115 = 968 μg/kg fish.
ERL (water) = 968 / 64 = 15 μg/L.

Input: TL_{hh} = 0.34 µg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 63 L/kg.
ERL (food) = (15.9 x 0.1 x 70) / 0.115 = 21 µg/kg fish.
ERL (water) = 21 / 63 = 0.33 µg/L.

4.12 Summary and discussion

The ERL based on direct ecotoxicity of 0.5 µg/L is based on a thorough literature survey performed by known experts. A final drinking water limit based on human toxicology has not been established yet. Depending on the input data, values between 1 and 56 µg/L may be derived. The DMR-target value is 0.1 µg/L, which is close to the ecotoxicological risk limit. The monitoring dataset is of good quality and shows a consistent pattern. The overall average of the 90^{th} percentile values from Dutch sampling stations over 2010 as reported by the RIWA is 0.1 µg/L. It should be noted that the Waterdienst and Water board Brabantse Delta found higher concentrations during screening monitoring in 2010 and 2011. Data of the Water board Roer and Overmaas confirm that concentrations in smaller water bodies may be higher than in larger rivers and waterways.
The 90^{th} percentile of concentrations in STP-effluents is 0.61-1.2 µg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.06-0.12 µg/L which is in accordance with measured data.
Based on the measured concentration of 0.1 µg/L, and ERL of 0.5 µg/L for direct ecotoxicity, the risk ratio is 0.2. Including fish consumption as a relevant route may result in a slightly higher risk ratio. Average concentrations in smaller water bodies may exceed the ERL based on direct ecotoxicity. Using the target value of 0.1 µg/L as proposed in the DMR-memorandum, the risk ratio is 1.0. Based on the most critical human toxicological threshold limit, the risk ratio is 0.1.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.5	µg/L
ERL secondary poisoning	-	
ERL drinking water	1-56	µg/L
ERL human fish consumption	0.32-15	µg/L
Environmental concentration	0.1	µg/L
Risk ratio	1.0	ERL DMR
	0.1-0.002	ERL DW
	0.2	ERL ECO

4.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90^{th} percentile concentrations are equal to or higher than the DMR-target value and refer to > 3 locations and multiple occasions; the ERL based on human toxicological data is probably close to the DMR-target value.
- relevant for ecology, because the risk ratio is > 0.1.

Recommendations

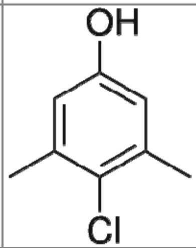
- consider inclusion in BKMW and/or Regeling monitoring KRW;
- continue monitoring.

5 Chloroxylenol

5.1 Introduction

Chloroxylenol is proposed by the Waterdienst as a potential relevant compound, because it is widely used as desinfectant in pharmaceutical products. The generic water quality standard for biocides in the BKMW (Dutch decree on water quality standards and monitoring [35]) is applicable to chloroxylenol.

5.2 Chemical identity

Name	Chloroxylenol
Chemical name	4-chloro-3,5-xylenol, 4-chloro-3,5-dimethylphenol
CAS number	88-04-0
EC number	201-793-8
Molecular formula	C8H9ClO
Molar mass	156.65
Structural formula	
SMILES code	Oc(cc(c(c1C)Cl)C)c1

5.3 Information on uses and emissions

In the USA, chloroxylenol is used as an antibacterial, germicide, antiseptic and in mildew prevention. It is applied as active component in deodorants, soaps, skin preparations for dermatological disorders, antiseptics, and as a preservative for aqueous functional fluids. It is also applied as antiseptic in human and veterinary hygiene [36]. It is not authorised for use as a biocide in the EU (see below). In the Netherlands, three products containing chloroxylenol are registered as human pharmaceutical under the trade name Dettol [4]. The GIP-database [5] does not contain use data. The compound is not included in the Pollutant Release and Transfer Register [6].

5.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Pre-registered, deadline for submission of dossier was 31/12/2010; not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not included in Annex I; to be phased out by 2009 for Pt 1-6
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as a human pharmaceutical in NL

The European Commission decided that the use of chloroxylenol as a biocide for Pt 1 to 6 had to be phased out by October, 2009, because no dossiers were submitted for review and/or all participants had discontinued their participation from the review program (Commission Decision 2008/809/EC). This applies to the use in Human hygiene biocidal products (Pt 1), Private area and public health area disinfectants and other biocidal products (Pt 2), Veterinary hygiene biocidal products (Pt 3), Food and feed area disinfectants (Pt 4), Drinking water disinfectants (Pt 5) and In-can preservatives (Pt 6).

5.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [μg/L]	Remark	Reference
NL	0.1	MKN, legal quality standard for biocides in surface water for abstraction of drinking water	[35]

5.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 315, 317, 319	harmonised classification	[8]
log K_{ow}	3.27	experimental	[36]
BCF	66 L/kg	estimated	[36]
	120 L/kg	estimated	[17]
Human toxicological threshold limit (TL_{hh})	not available		

5.7 Environmental concentrations

5.7.1 Netherlands

During screening monitoring in 2010, concentrations at Lobith were below the reporting limit. Chloroxylenol was detected in the Meuse, maximum concentration was 0.08 μg/L (Marcel Kotte, pers. comm.).

Chloroxylenol was not detected above the reporting limit at the RIWA sampling point Heel in 2008 and 2010 [12].

5.7.2 Information from other countries

Based on a paper by Thomas et al. [37], it is stated in HSDB [36] that chloroxylenol was detected in 3 out of 10 estuaries in the United Kingdom in concentrations ranging from 581 to 4 μg/L. However, in the original paper only the figure of 581 μg/L could be found and this refers to an estimated concentration that was calculated on the basis of bioassays, using a toxic units approach [37].

5.8 Removal upon water treatment

Chloroxylenol is not put forward as a specific drinking water relevant substance by the RIWA.

5.9 Environmental risk limits based on direct ecotoxicity

Established or proposed risk limits for direct ecotoxicity are not available. The following ecotoxicity data are available:

Taxon	Species	L/EC_{50} Value [µg/L]	Remark	Reference
Crustacea	*Daphnia magna*	7700	48 h	[38]
	Daphnia magna	2700	48 h	[38]
	Thermocyclops oblongatus	170	24 h	[39]
Fish	*Oncorhynchus mykiss*	360	96 h	[38,40]
	Oncorhynchus mykiss	760	96 h	[38]
	Lepomis macrochirus	2700	96 h	[38]
	Lepomis macrochirus	1600	96 h	[38]
	Poecilia reticulata	1640	24 h	[39]

Since data on algae are missing, the base set is not complete. Algae probably represent a sensitive species group, since they belong to, or are most related to the target organisms. According to the WFD/REACH-guidance it is therefore not possible to derive acute or chronic water quality standards or a chronic PNEC. According to the Dutch methodology for derivation of indicative environmental risk limits [13], in case endpoints are available for two of the base-set species, a chronic ERL may be derived by putting an assessment factor of 3000 to the lowest L/EC_{50}. This results in an ERL of 0.06 µg/L.

5.10 Environmental risk limits based on secondary poisoning

The following information is available from US EPA [41]:
'A developmental toxicity study was conducted in Sprague Dawley rats with dose levels of 0, 100, 500, or 1000 mg/kg given by gavage on gestation days 6-15. The maternal No Observed Effect Level (NOEL) was 100 mg/kg/day. The maternal Lowest Observed Effect Level (LOEL) was 500 mg/kg/day, based on decreased weight gain and food consumption. There were deaths at the high dose. The NOEL for developmental toxicity was 1000 mg/kg/day, the highest dose'.

Using a conversion factor of 20, the NOEL of 100 mg/kg d is equivalent to 2000 mg/kg fd. With an assessment factor of 90, the $PNEC_{oral}$ is 22 mg/kg fd. With a BCF of 120 L/kg, the corresponding ERL for water is 0.185 mg/L = 185 µg/L.

5.11 Environmental risk limits based on human toxicology

5.11.1 Surface water for drinking water abstraction

There is some information on human toxicology available via HSDB [36] and US EPA [41]. Evaluation by experts is needed to establish a human toxicological threshold limit. It is expected, however, that this route will be less critical than direct ecotoxicity.

5.11.2 Surface water for fish consumption

See section 5.11.1 above.

5.12 Summary and discussion

There are not enough monitoring data available to evaluate the potential risks of chloroxylenol. The ERL for direct ecotoxicity is derived with a high assessment factor. However, even considering the option that additional data would allow for a lower assessment factor, the resulting ERL would most likely still be in the low µg/L range.

MKN BKMW	0.1	µg/L
ERL direct ecotoxicity	0.06	µg/L
ERL secondary poisoning	185	µg/L
ERL drinking water	-	µg/L
ERL human fish consumption	-	µg/L
Environmental concentration	max. 0.08	µg/L
Risk ratio	-	MKN BKMW
	-	ERL ECO

5.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90th percentile concentrations are lower than the DMR-target value; a standard for biocides is already included in the BKMW;
- potentially relevant for ecology, because the risk ratio is > 1, but detected at one location only in 2010.

Recommendation

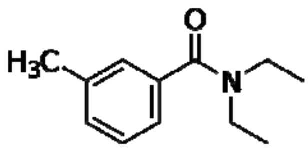
- continue monitoring.

6 DEET

6.1 Introduction

DEET is included as a drinking water relevant substance in Annex III of the BKMW [35]. DEET is present in surface water used for drinking water abstraction. Furthermore, being a pesticide DEET is considered as substance that may rise public concern. The risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies. The Waterdienst has put forward DEET as a potential specific pollutant because of the widespread use as insect repellent by consumers and observed occurrence in STP-effluents.

6.2 Chemical identity

Name	DEET
Chemical name	n,n-diethyl-3-methylbenzamide
CAS number	134-62-3
Molecular formula	C12H17NO
Molar mass	191.27
EC number	205-149-7
Structural formula	
SMILES code	CCN(CC)C(=O)C1=CC(=CC=C1)C

6.3 Information on uses and emissions

N,N-Diethyl-meta-toluamide, abbreviated DEET, is a slightly yellow oil. It is the most common active ingredient in insect repellents. It is intended to be applied to the skin or to clothing, and is primarily used to repel mosquitoes. In particular, DEET protects against tick bites, preventing several rickettsioses, tick-borne meningoencephalitis and other tick-borne diseases such as Lyme disease. It also protects against mosquito bites which can transmit dengue fever, West Nile virus, eastern equine encephalitis, and malaria. There are no products registered for biocidal use in the Netherlands [42], but a number of over-the-counter products contain DEET. The compound is not included in the Pollutant Release and Transfer Register [6].

6.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not included in Annex I
Biocides (98/8/EC)	Included in Annex I
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	D: Classified as water hazardous class 2 [14]

6.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	0.1	legal MKN value for pesticides/biocides in surface water for abstraction of drinking water	[35]
EU	41	PNEC, EC_{50} for algal growth rate with AF 1000	[43]
D	71.3	WQK, provisional value, AF 1000	[44]
	0.1	target value for biocides in surface water for abstraction of drinking water	[7]

6.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 315, 319, 412	harmonised classification	[8]
BCF	22 L/kg	estimated value	[43]
Human toxicological threshold limit (TL_{hh})	0.75 mg/kg bw.d	AEL based on oral exposure rat	[43]

6.7 Environmental concentrations

6.7.1 Netherlands

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
2006	<	0.05	<	<	0.046	13 (Brakel)	[12]
2007	<	0.04	<	<	0.036	13 (Brakel)	[12]
2008	<	0.04	<	<	0.036	13 (Brakel)	[12]
	<	0.05	<	0.0208	0.05	13 (Keizersveer)	
	<	0.02	<	<	<	13 (Nieuwegein)	
2009	<	0.04	<	<	0.036	13 (Brakel)	[12]
	<	0.06	<	0.0208	0.056	13 (Keizersveer)	
	<	<	<	<	<	13 (Lobith)	
	<	0.02	<	<	0.02	13 (Nieuwegein)	
	<	0.04	<	<	0.036	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
2009		1.29		0.19		23 occasions during screening	[30]
2010	<	0.06	<	<	0.056	13 (Namêche)	[12]
	<	0.07	<	<	0.052	13 (Luik)	
	<	0.05	*	0.0225	*	4 (Heel)	
	<	0.03	<	<	0.03	13 (Brakel)	
	<	0.07	<	0.0223	0.062	13 (Keizersveer)	
	<	<	<	<	<	12 (Lobith)	
	<	<	<	<	<	13 (Nieuwegein)	
	<	0.03	<	<	0.026	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	<	<	<	<	10 (Stellendam)	

The overall average of the reported 90^{th} percentile concentrations in Dutch sampling points of the RIWA over 2010 is 0.04 µg/L.

During screening monitoring for pesticides in the Meuse catchment area in 2007, DEET was among the most frequently detected compounds [45]. The highest concentration of 25.7 µg/L was found by the Water board Peel and Maasvallei.

Based on a comparison of monitoring data from 11 water boards over 2000-2009, DEET was identified as a substance of concern since risk limits were exceeded in 5-15% of the cases (Gezamenlijk meetnet bestrijdingsmiddelen 2000-2009). This was based on an unofficial indicative MPC-value of 0.11 μg/L, which is also used in the *Bestrijdingsmiddelenatlas* ('Pesticide atlas', www.bestrijdingsmiddelenatlas.nl). The PNEC used for biocide authorisation is much higher (see above). Wetterskip Fryslân, which is one of the participants of this investigation, provided monitoring data for 2009 and 2010. The results are summarised below.

Monitoring location	Year	Average (range) [μg/L]	n samples
1	2009	0.044 (0.01-0.11)	7
2	2009	0.053 (0.02-0.13)	9
3	2009 2010	0.036 (0.01-0.12) 0.01, 0.17	5 2
4	2009	0.03 (0.01-0.06)	8
5	2009 2010	0.062 (0.01-0.14) 0.053 (0.01-0.08)	10 6
6	2009 2010	0.056 (0.02-0.13) 0.03, 0.06	5 2
7	2009 2010	0.03, 0.04 0.04, 0.08	2 2
8	2009	0.28 (0.03-0.62)	12
9	2009	0.035 (0.02-0.06)	8
10	2010	0.12, 0.01	2
11	2010	0.17 (0.02-0.65)	5
12	2010	0.055 (0.01-0.09)	6
13 – 23	2010	0.05 – 1.3	single measurements for 10 different sampling locations

Monitoring data for groundwater and surface water were provided by the Water board Hollandse Delta (Province of South-Holland). At the WFD-monitoring locations, concentrations of DEET ranged from <0.01 to 0.05 μg/L in 2008-2009. This is consistent with the RIWA data. Data from the regular pesticide monitoring program were also provided, results for 2009 and 2010 are summarised here. About 90 locations were sampled three or four times, the majority of samples showed concentrations below the reporting limit. In 2009, DEET was detected more than once at four different locations, concentrations ranged from 0.04 to 4.7 μg/L. In 2010, concentrations between 0.8 and 4.9 μg/L were found at those particular locations and two additional locations showed concentrations between 0.02 and 0.74 μg/L.

Water board Roer and Overmaas (Province of Limburg) provided monitoring data for 2007-2010, results for 2009 and 2010 are summarised here. In 2009, DEET was detected at 5 out of 18 locations on one or more sampling dates. Concentrations ranged from 0.1 to 0.6 μg/L. In 2010, DEET was analysed at 25 locations, 7 of which refer to STP-effluents (see below). Concentrations were below the reporting limit in the majority of cases, including those locations at which DEET was detected in 2009, except for one location with concentrations of 0.5 and 0.22 μg/L in March and May, 2010.

For 2010, the Bestrijdingsmiddelenatlas reports that there are two locations with concentrations > five times the indicative MPC, eight locations with concentrations > two times the MPC and nine locations at which the MPC is exceeded. As indicated above, the indicative MPC of 0.11 μg/L is not officially set.

In 2011, Water board Brabantse Delta (western part of the Province of North-Brabant) included DEET in a screening monitoring program in which 12 locations were sampled twice (May and June). At three locations, DEET was detected once at concentrations of 0.02–0.03 µg/L, which is at or just above the reporting limit (0.02 µg/L). This is consistent with the RIWA data. At one location, DEET was detected in both samples, concentrations were 0.08 and 0.14 µg/L.

Monitoring data for 2011 were provided for six water boards which have their samples analysed by Water board Groot Salland. DEET was detected 18 times on 6 locations, concentrations ranged from 0.01 to 0.09 µg/L, average was 0.03 µg/L. These concentrations are consistent with the RIWA data.

Concentrations in STP-effluents are 0–2.6 µg/L, 90^{th} percentile 0.45 µg/L (WD data). Water board Roer and Overmaas report concentrations in STP-effluent of 0.1-0.41 µg/L.

6.7.2 Other information

DEET is found in STP effluents and sea water in Norway (Weigel et al., 2004). An STP influent concentration of 0.21 µg/L is reported, effluent concentrations were 0.01-0.13 µg/L. Concentrations in seawater are in the ng/L range. The highest predicted environmental concentration (PEC) in water in the biocides risk assessment is 30 µg/L [43].

6.8 Removal upon water treatment

Based on a log K_{ow} of 2.26, VP of 0.00331 and BIOWIN3 value of 2.6474 (weeks to months), DEET is considered difficult to remove by current methods for surface water treatment (0-40% removed). Reduction of the level of purification treatment will not be possible.

6.9 Environmental risk limits based on ecotoxicity

For the present assessment, the PNEC of 41 µg/L as used in the biocides assessment is selected.

6.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

6.11 Environmental risk limits based on human toxicology

6.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 75 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (75 x 0.1 x 70) / 2 = 263 mg/L

The target value for biocides in surface water for abstraction of drinking water as proposed in the DMR-memorandum is 0.1 µg/L. The water quality standard for biocides as included in the BKMW is also 0.1.

6.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

6.12 Summary and discussion

Although based on a European evaluation, there is considerable uncertainty related to the PNEC of 41 µg/L from the biocides dossier. DEET is an insect repellent, for which the base set organisms (algae, *Daphnia*, fish) may not represent the most sensitive taxa. Furthermore, there are no chronic data included in the dataset. It is assumed that using the highest assessment factor of 1000 on an acute L/EC_{50} leads to a PNEC that is protective. It is hard to judge to what extent additional data would influence the PNEC. If an acute L/EC_{50} for insects would be present, a lower assessment factor of 100 would be allowed

instead of the factor of 1000 that has been used now. This means that the same PNEC would be derived if an insect has an EC_{50} of about 4 mg/L, which is about 20 times lower than the EC_{50} for *Daphnia magna* (75 mg/L). For a compound specifically aimed at insects, this is not unrealistic. It should be noted, however, that the compound is a repellent rather than an insecticide. Additional data would probably not change the PNEC to a great extent, although the background of the unofficial indicative MPC should be retrieved to check this.
The monitoring data of the RIWA indicate that the compound is not often detected in larger waterways, while the limit of quantification (0.02-0.05 µg/L) is sufficiently low as compared to the drinking water limit for biocides of 0.1 µg/L. The overall average of the 90^{th} percentile concentrations is 0.04 µg/L. Data from water boards are comparable with the RIWA data as far as WFD-monitoring locations are concerned. For other water bodies, higher concentrations are reported. The highest concentration of over 25 µg/L was found during screening monitoring in the Meuse area in 2007. Recent data indicate lower levels, e.g. concentrations up to 4.7-4.9 µg/L are reported for 2009 and 2010. In addition, there are relatively few locations where concentrations are above the reporting limits on consecutive sampling dates. Most locations sampled by Wetterskip Fryslân have concentrations comparable to the 90^{th} percentile of the RIWA. However, there are also locations at which levels are consistently higher, but the averages are still much lower than the PNEC from the biocides dossier. The Waterdienst found a maximum level of 1.29 µg/L during screening monitoring in 2009.
The 90^{th} percentile of concentrations in STP-effluents is 0.45 µg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.05 µg/L which is in accordance with measured data.
Based on the measured concentration of 0.04 µg/L (average of 90^{th} percentile concentrations in 2010 reported by the RIWA), and the environmental quality standard of 0.1 µg/L for surface water intended for the abstraction of drinking water, the risk ratio is 0.2. Based on the ERL for direct ecotoxicity, the risk ratio is 0.001. This ratio may change when data on insects would be available, but it is doubtful that a different PNEC would approach the measured concentrations.

MKN BKMW	0.1	µg/L
ERL direct ecotoxicity	41	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	263,000	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.04	µg/L
Risk ratio	0.4	MKN BKMW
	0.001	ERL ECO

n.r. = not relevant

6.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- already included in the BKMW as a drinking water relevant compound;
- not relevant for ecology, because the risk ratio is <0.01 on the basis of the biocides PNEC; indicative MPC suggests otherwise.

Recommendations

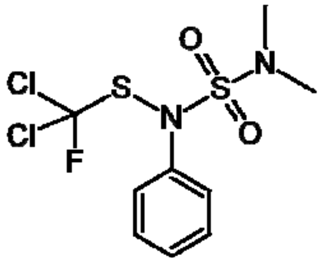
- keep in BKMW;
- continue monitoring;
- check background of indicative MPC used in Bestrijdingsmiddelenatlas.

7 Dichlofluanid

7.1 Introduction

Dichlofluanid is proposed by the Waterdienst as a potential relevant compound, because of its widespread use as biocide. It is detected in surface water and present in harbours. Dichlofluanid has been considered as a candidate priority substance under the Water Framework Directive [46]. The generic water quality standard for biocides in the BKMW [35] is applicable to dichlofluanid.

7.2 Chemical identity

Name	Dichlofluanid
Chemical name	N-(Dichlorofluoromethylthio)-N',N'-dimethyl-Nphenylsulfamide, Methanesulfenamide, 1,1-dichloro-N-[(dimethylamino)sulfonyl]-1-fluoro-N-phenyl-
CAS number	1085-98-9
EC number	214-118-7
Molecular formula	C9H11Cl2FN2O2S2
Molar mass	333.2
Structural formula	
SMILES code	CN(C)[S](N(C1=CC=CC=C1)SC(Cl)(Cl)F)(=O)=O

7.3 Information on uses and emissions

Dichlofluanid is used as a fungicidal biocide in anti-fouling paints (Pt 21), wood preservatives (Pt 8) and film preservatives (Pt 7). In the Netherlands, the only authorised products are for Pt 7. For some anti-fouling paints, an expiration period existed until 2010. The European evaluation of dichlofluanid for use in anti-fouling is scheduled for 2012. Actual use figures are not available. Estimated emissions to sewage and surface water have increased from 125 kg in 1990 to 9921 kg in 2009 [6].

7.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not included
Biocides (98/8/EC)	Included in Annex I for Pt 8; assessment for Pt 7 and 21 is pending
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as biocide in NL for Pt 7

The draft dossier for evaluation of dichlofluanid as candidate priority substance under the WFD was based on the biocides risk assessment of 2006 [47]. The deadline for submission of the European evaluation of dichlofluanid for use as anti-fouling was March, 2012 (Rapporteur Member State United Kingdom).

7.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	0.1	legal MKN value for pesticides/biocides in surface water for abstraction of drinking water	[35]
NL	0.03[1]	indicative MPC_{water}	[48]
NL	190 µg/kg	MPC for sediment	[49]
EU	0.27	PNEC, based on direct ecotoxicity	[47]
EU	0.26	AA-EQS, based on direct ecotoxicity	[46]
EU	0.1	MAC-EQS, based on direct ecotoxicity	[46]
	0.1	target value for biocides in surface water for abstraction of drinking water	[7]

1: most likely not approved by Stuurgroep Stoffen, since not included on www.rivm.nl/rvs

7.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H317, 319, 332, 400	harmonised classification	[8]
log K_{ow}	3.5		[47]
BCF	72 L/kg	experimental; whole fish	[47]
Human toxicological threshold limit (TL_{hh})	0.35 mg/kg bw.d	Acceptable Daily Intake (ADI) based on fluorosis	[47]

7.7 Environmental concentrations

7.7.1 Dichlofluanid

Monitoring data for 2007-2010 were provided by the Water board Roer and Overmaas (Province of Limburg). In 2007, dichlofluanid was found on four locations during screening monitoring (see also below). Concentrations ranged from 0.02 to 0.057 µg/L. In 2008-2010, the reporting limit of 0.01-0.03 µg/L was never exceeded.

In 2007, dichlofluanid was included in the screening monitoring campaign for pesticides in the Meuse catchment area [45]. Dichlofluanide was detected 51 times above the detection limit, in five cases the indicative MPC of 0.03 µg/L was exceeded. The above reported values for Roer and Overmaas belong to these cases.

Dichlofluanid was detected once in 2008 by Wetterskip Fryslân at a concentration of 0.06 µg/L.

In 2010, dichlofluanid was not detected at the RIWA sampling points at concentrations above the limit of quantification of 0.03 µg/L [12,50]. The Waterdienst did not detect dichlofluanid either, main metabolite DMSA was detected at a maximum concentration of 0.005 µg/L (Marcel Kotte, pers. comm.).

In 2011, dichlofluanid was not detected above the reporting limit of 0.02 µg/L during screening monitoring by the Water board Brabantse Delta. Six water boards which have their samples analysed by Water board Groot Salland did not detect dichlofluanid either.

In the Bestrijdingsmiddelenatlas, average concentrations of 8–10 ng/L are reported for 2009. This is most likely based on calculations in which for non-detects half of the detection limit is used as result.

7.7.2 Metabolite DMSA

Dichlofluanid rapidly degrades in water/sediment systems with a DT_{50} of 1-3 h. Hydrolysis is fast, with a DT_{50} of about 1 day at 20 °C, pH 7. Degradation hampers the analysis in water samples. Analysis of its main metabolite N,N-dimethyl-N'-phenylsulfamide (DMSA) in water may therefore be used as an indirect proof of the presence of dichlofluanid in water.

DMSA was detected in a monitoring survey that was performed by Kiwa Water cycle Research from August to December 2007 (Kleinnenhuis and Puijker, 2008, cited in [51]. DMSA was detected at concentrations of <10 ng/L to ca. 1 µg/L, highest levels were found in harbours. Assuming that all DMSA originates from dichlofluanid, the equivalent concentrations if dichloflunanid amount to <17 ng/L to 1.7 µg/L.

In 2009, water samples from harbours were analysed for DMSA, as part of the development of an analytical method [52]. DMSA was detected at all seven sampling locations, four of which had concentrations above the reporting limit (0.025 µg/L). The 90^{th} percentile of these measured concentrations was 0.13 µg/L. Assuming that all DMSA originates from dichlofluanid, the equivalent concentration of dichlofluanid is 0.22 µg/L. Reported concentrations are not corrected for recovery of the analytical method of about 50%, so concentrations might have been twice as high.

7.7.3 Predicted environmental concentrations

In 2007, several antifouling products have been evaluated by Ctgb, the Dutch authorisation board for plant protection products and biocides [53]. In the assessments, a 21-days PEC of 0.22 µg/L is used initially. The notifier has submitted exposure assessments that were used for the European Annex I listing for dichlofluanid in antifoulings, in which a 21-days PEC of 0.044 µg/L is used. The EU assessment for Pt 21 will become available in 2012.

7.8 Removal upon water treatment

Dichlofluanid is not put forward as a specific drinking water relevant substance by the RIWA. Since the compound is a biocide, it is included in the BKMW.

In the draft EQS-dossier it is mentioned that the main metabolite of dichlofluanid, N,N-dimethyl-N'-phenylsulfamide (DMSA), can further degrade to N,N-dimethylsulfamide. This compound, which is also identified a metabolite of tolylfluanid, can react with ozone during preparation of drinking water. This reaction results in N-nitrosodimethylaamine (NDMA), which is carcinogenic. For this reason, the Annex I listing of tolylfuanid under Directive 91/414/EC was withdrawn by Directive 2010/20/EU in March 2010. It is not known, however, whether the formation of N,N-dimethylsulfamide from dichlofluanid is of equal importance as observed for tolylfluanid.

7.9 Environmental risk limits based on direct ecotoxicity

The indicative MPC of 0.03 µg/L is a factor of 10 lower than the PNEC from the biocides assessment (see section 7.5). For the present assessment, the PNEC of 0.27 µg/L from the EU biocides risk assessment report is selected.

7.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

7.11 Environmental risk limits based on human toxicology

7.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.35 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.35 x 0.1 x 70) / 2 = 1.2 mg/L = 1200 µg/L.

The proposed target value for biocides according to the DMR-memorandum is 0.1 µg/L, in line with EU Directive 98/83/EC. This limit is also implemented in the BKMW.

7.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

7.12 Summary and discussion

The PNEC for direct ecotoxicity of 0.27 µg/L is established during the review for Annex I listing and is considered adequate. Dichlofluanid itself was not detected in larger surface waters upon monitoring. It is possible that because of the fast degradation, the substance is indeed not present in the water phase. It is also possible that it is degraded during sampling, transportation or analysis. During a screening monitoring campaign in the Meuse catchment area in 2007, dichlofluanid was detected at several locations at concentrations above 0.03 µg/L. Some of these locations were located in the Roer and Overmaas-area, where dichlofluanid was not detected anymore in 2008-2010. It was detected once by Wetterskip Fryslân in 2008 at 0.06 µg/L.
DMSA, the main metabolite of dichlofluanid, is detected in surface water at levels of up to 1 µg/L. DMSA is far less toxic than its parent, acute L/EC_{50} values for fish and daphnids are in the 100 mg/L-range, the long-term NOEC for fish is around 10 mg/L.
Assuming that all DMSA originates from dichlofluanid, corresponding concentrations of dichlofluanid amount to 1.7 µg/L. The question arises, however, if it is reasonable to assume that long-term exposure of aquatic organisms has occurred. Leaching from paint is a continuous process and as a biocide, the compound has been designed to be toxic. It is most likely, however, that the presence of the active substance is restricted to a small layer near the treated surface, and that for the remainder of the water only DMSA is relevant. It is expected that the European biocides risk assessment will give more insight into the PEC for small harbours. The screening campaign in the Meuse area in 2011 will probably also provide more information on occurrence of dichlofluanid. Furthermore, the issue of nitrosamine formation resulting from ozone treatment will be subject of the risk assessment.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.27	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	1200	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	-	µg/L
Risk ratio	-	DMR
	-	ECO

7.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not detected in large surface waters; a standard for biocides is already included in the BKMW;
- not relevant for ecology, because the compound has not been detected in surface water recently, ecological risk limit is relatively low.

Recommendations

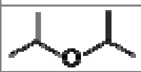
- postpone further actions until results of the screening monitoring in the Meuse area and the EU risk assessment for anti-foulings are available.

8 Diisopropylether

8.1 Introduction

Diisopropylether (DIPE) is proposed by the RIWA as a drinking water relevant compound because it is considered toxicologically relevant and frequently present in surface water used for drinking water abstraction.

8.2 Chemical identity

Name	Diisopropylether
Chemical name	isopropylether, 2,2'-oxybispropaan, 2-isopropoxypropaan, DIPE
CAS number	108-20-3
EC number	203-560-6
Molecular formula	C6H14O
Molar mass	102.175
Structural formula	
SMILES code	CC(C)OC(C)C

8.3 Information on uses and emissions

Diisopropylether is used as solvent for mineral and animal oils and fats, wax, and a number of natural resins. It is also added as odour to natural gas. Chemical manufacturers also use it to synthesize and analyze chemicals.
In the REACH dossier [8], use by consumers as fuel is also indicated. The compound is not included in the Pollutant Release and Transfer Register [6].

8.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	

8.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	21	indicative MPC, based on total concentrations; based on human exposure, see section 8.9	[49]
EU	190	PNEC, based on EC_{50} *Daphnia magna*, AF 1000	[8]
	1	target value for anthropogenic compounds in surface water for abstraction of drinking water	[7]

8.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H336	harmonised classification	[8]
log K_{ow}	1.88	estimated	[1]
	1.52	experimental	[1]
BCF	6 L/kg	estimated	[8]
	3.9 L/kg	estimated	[17]
Human toxicological threshold limit (TL_{hh})	0.2 mg/kg bw.d	US EPA RfD for ethylether	[54]

8.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
2006	0.27	5.1	1	1.74	4.66	13 (Eijsden)	[12]
	<	1.6	<	<	<	149 (Heel)	
	<	0.11	0.02	0.0354	0.106	13 (Brakel)	
	<	0.87	0.11	0.16	0.61	13 (Keizersveer)	
	<	<	<	<	<	13 (Lobith)	
	<	<	<	<	<	26 (Nieuwegein)	
	<	0.04	<	<	0.028	13 (Nieuwersluis)	
	<	<	<	<	<	15 (Andijk)	
	<	0.03	<	<	0.027	12 (Stellendam)	
2007	0.17	7.9	1.6	3.01	7.5	13 (Eijsden)	[12]
	<	<	<	<	<	149 (Heel)	
	<	0.06	<	<	0.048	13 (Brakel)	
	<	2.6	0.28	0.38	0.8	27 (Keizersveer)	
	<	<	<	<	<	13 (Lobith)	
	<	<	<	<	<	28 (Nieuwegein)	
	<	0.058	<	<	0.0436	12 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.16	<	0.0208	0.116	13 (Stellendam)	
2008	0.03	11	3.9	4.31	10.4	13 (Eijsden)	[12]
	<	<	<	<	<	148 (Heel)	
	<	0.07	0.02	0.0225	0.058	12 (Brakel)	
	<	1.9	0.425	0.556	1.33	26 (Keizersveer)	
	<	0.09	<	0.0138	0.066	13 (Lobith)	
	<	<	<	<	<	16 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.24	<	0.0454	0.21	12 (Stellendam)	
2009	9.14	1.93	2.65	9.01	9.01	12 (Liège)	[12]
	<	12	1.4	2.63	9.4	13 (Eijsden)	
	<	0.32	<	0.0546	0.26	13 (Brakel)	
	<	2.5	0.14	0.28	0.66	26 (Keizersveer)	
	<	0.01	<	<	<	13 (Lobith)	
	<	<	<	<	<	13 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.15	<	0.0246	0.11	13 (Stellendam)	
2010	<	<		<		8 (Namêche)	[12]
	<	6.57	2.41	3.01	6.49	10 (Liège)	
	0.03	8.1	1	1.56	5.5	13 (Eijsden)	
	0.06	1.6	0.44	0.512	1.4	13 (Heel)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
	<	0.1	<	<	0.072	13 (Brakel)	
	<	1.3	0.15	0.278	0.76	26 (Keizersveer)	
	<	<		<		9 (Lobith)	
	<	0.03	<	<	0.022	13 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	0.03	<	<	0.022	13 (Andijk)	
	<	0.06	<	0.0142	0.06	13 (Stellendam)	

From the RIWA data it is apparent that concentrations in the upstream Meuse-area are high as compared to the other sampling points. The overall average of the 90th percentile concentrations in 2010 is 1.79 µg/L when considering all sampling stations, and 5.0 µg/L considering Liège and Eijsden only. This indicates that a source of DIPE is located upstream. For this evaluation, the overall average of the 90th percentile concentration at Dutch sampling points of the RIWA over 2010 is used, this concentration is 1.1 µg/L. It should be noted that this value is mainly determined by the relatively high concentrations at Eijsden, Heel and Brakel.

During screening monitoring in 2010, DIPE was not detected by the Water board Hollandse Delta (Province of South-Holland) above the reporting limit of 0.01 µg/L (two locations, one sampling date).

8.8 Removal upon water treatment

Based on a log Kow of 1.88, VP of 151 and BIOWIN3 value of 2.9647 (weeks to months), DIPE is not considered difficult to remove by simple surface water treatment because due to its volatility it is easily removed by aeration. However, DIPE has a low odour threshold of <10 µg/L. This is relevant to drinking water production (Exxon Moblie and Shell, 2005) in view of the measured concentrations of 5-10 µg/L at Liège and Eijsden in 2009-2010.

8.9 Environmental risk limits based on direct ecotoxicity

The indicative MPC was derived by RIVM in 2007 [54] by order of the former RIZA, now the Waterdienst. It was based on a human risk limit of 0.2 mg/kg bw.d using the program HUMANEX. This program is no longer used, and the derivation of human-based risk limits for water would now be performed according to the methodology of the Water Framework Directive (WFD), i.e. considering fish consumption for derivation of the general water quality standard and a separate assessment for the use of surface water for drinking water abstraction. Fish consumption is not relevant in view of the low bioaccumulation. The indicative $MPC_{eco, water}$ is 91.7 µg/L, based on an LC_{50} of 91.7 mg/L for *Pimephales promelas* with an assessment factor of 1000. This LC_{50} is also included in the REACH summary dossier, but although it was assigned Ri2 (reliable with restrictions), it was apparently not used for PNEC derivation. In addition to the data used for the indicative MPC, the REACH-dossier contains EC_{50}-values for algae and *Daphnia*. This does not influence the height of the indicative $MPC_{eco, water}$. Moreover, a similar MPC would be derived according to the WFD-methodology, provided that the underlying studies appear to be reliable upon evaluation. For the present evaluation, the $MPC_{eco, water}$ of 91.7 µg/L is used.

8.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

8.11 Environmental risk limits based on human toxicology

8.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.2 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.2 x 0.1 x 70) / 2 = 0.700 mg/L = 700 µg/L.

For anthropogenic organic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

8.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

8.12 Summary and discussion

The existing data indicate that the ecotoxicity of diisopropylether is relatively low. Since no chronic data are available, the indicative $MPC_{eco,\ water}$ is derived with an assessment factor of 1000. Diisopropylether acts via narcosis, and it is generally assumed that a factor of 10 covers the difference between acute L/EC_{50} and chronic NOEC. This means that the NOEC for fish will most likely be around 10 mg/L, and that an ERL based on chronic data would most likely be in the low mg/L range. It is doubtful, however, that additional chronic data will be retrieved, since no references were found in the major data sources.
Monitoring data show a consistent pattern of relatively high concentrations in the upstream Meuse area, with levels up to 5-10 µg/L at Liège and Eijsden, but relatively low concentrations and non-detects downstream. The average of 90^{th} percentile concentrations in 2010 for Dutch sampling points reported by the RIWA is 1.1 µg/L, which is higher than the DMR-target value. Comparing the measured concentrations with the drinking water limit based on human toxicological data, the risk ratio is 0.002. Based on the ERL for direct ecotoxicity, the risk ratio is 0.01.

ERL DMR-memorandum	1	µg/L
Indicative $MPC_{eco,\ water}$ direct ecotoxicity	91.7	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	700	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	1.1	µg/L
Risk ratio	1.1	ERL DMR
	0.002	ERL DW
	0.01	ERL ECO

8.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90^{th} percentile concentrations are higher than the DMR-target value at max. 3 locations in one year, but much lower than the drinking water limit based on human toxicology; presence of diisopropylether might be related to an upstream source in Belgium;
- not relevant for ecology, because the risk ratio is 0.01 based on conservative risk limit.

Recommendations

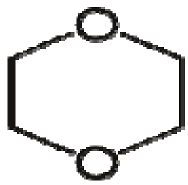
- continue monitoring;
- investigate emission sources Meuse.

9 1,4-Dioxane

9.1 Introduction

1,4-Dioxane has been put forward by the RIWA as a drinking water relevant compound, because it is toxicologically relevant and frequently present in surface water used for drinking water abstraction. The compound is included in the list of candidate substances for the monitoring program for 2014 of the International Commission for the Protection of the Rhine [2].

9.2 Chemical identity

Name	1,4-dixoaan
Chemical name	p-dioxaan; dioxaan; 1,4-diethyleendioxide; diethyleenether; dioxyethyleenether
CAS number	123-91-1
EC number	204-661-8
Molecular formula	C_4H8O_2
Molar mass	88.12
Structural formula	
SMILES code	C1COCCO1

9.3 Information on uses and emissions

1,4-Dioxane has a great variety of applications. Because of its physical-chemical properties it is mainly used as a processing solvent (waxes, fat, lacquers, varnishes, cleaning and detergent preparations, adhesives, cosmetics, deodorant fumigants, emulsions and polishing compositions, pulping of wood). It is also used as an extraction medium for animal and vegetable oils and as a laboratory chemical (eluent in chromatography) and in plastic, rubber, insecticides and herbicides. Other uses are for measuring optical activity, for cryoscopic determination and in the manufacturing of membrane filters [55]. In the Netherlands, it is used at at least one location (Dordrecht). The compound is not included in the Pollutant Release and Transfer Register [6].

9.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Yes, final EU-RAR available [55]
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as pharmaceutical in NL D: Classified as water hazardous class 2 [14]

9.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
EU	57500	PNEC, NOEC *Mycrocystis aeruginosa* with AF 10	[55]
EU	10000	PNEC, NOEC *Oryzias latipes* with AF 10	[8]
	1.0	target value for anthropogenous substances without a known specific action	[7]

9.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H319, 335, 351	harmonised classification	[8]
log K_{ow}	-0.32	estimated	[55]
BCF	0.2-0.7 L/kg		[55]
Human toxicological threshold limit (TL_{hh})	0.1 mg/kg bw.d		[56]
	0.011 mg/kg bw.d		[10]
	0.03 mg/kg bw.d	oral NOEAL 9.6 mg/kg bw.d; AF 300	[57]

9.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2010	<	1.2	0.74		8 samples at Lobith	[12]

The EU-RAR [55] reports measured concentrations of 1-10 µg/L in surface water in the Province Drenthe, and 0.5 µg/L in drinking water in 1997. This relates to a PET production facility in Emmen, which discharged until 1997.

9.8 Removal upon water treatment

Based on a log K_{ow} of -0.32, VP of 40.6 and BIOWIN3 value of 2,9871 (weeks to months), 1,4-dioxane is considered difficult to remove by current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

9.9 Environmental risk limits based on direct ecotoxicity

The PNEC as proposed by the registrant is probably based on a NOEC that in fact is a ≥ value, since in another study with fish no effects were found at concentrations up to 103 mg/L. For the present assessment, the PNEC from the EU-RAR of 57.5 mg/L is selected.

9.10 Environmental risk limits based on secondary poisoning

Not relevant.

9.11 Environmental risk limits based on human toxicology

9.11.1 Surface water for drinking water abstraction

Schriks et al. [10] derived a provisional guideline value of 30 µg/L, based on an oral slope factor of 0.011 mg/kg bw.d, and a specific cancer risk value of 10^{-5}. NOTE: A 10-times lower cancer risk of 10^{-6} is common practice under the WFD. A provisional drinking water limit of 3 µg/L was used in 1997 [56]. Relevant mail from the author (in Dutch) is copied below.

Bijgaand het ad hoc advies uit 1997. De uitkomst was een voorlopige orale MTR van 0.1 mg/kg lg/dag. Door de toenmalige Regionale Inspectie van Volksgezondheid voor de Milieuhygiëne voor Noord Nederland (de opdrachtgever voor het ad hoc-advies) is destijds op basis van het VR (onze MTR gedeeld door 100) een drinkwaternorm van 3 µg/liter afgeleid.

Bij ons advies hebben we een draft-versie van de RAR gebruikt. Afgezet tegen de informatie zoals uiteindelijk opgenomen in de RAR behoeft de destijds afgeleide voorlopige MTR geen bijstelling, lijkt mij. Echter de gepubliceerde US-EPA-beoordeling uit 2010 maakt duidelijk dat er belangrijke nieuwe Japanse studies zijn (o.a. orale 2 jaarsstudies in rat en muis, 2 jaar inhalatie rat). Deze gegevens zouden voor een geactualiseerde MTR nader bekeken moeten worden. Er is sinds het verschijnen van de RAR ook een in vivo genotoxiteitsstudie verschenen met een positief resultaat. Dat resultaat zou repercussies kunnen hebben voor de eindconclusie inzake genotoxiciteit (dit is belangrijk voor de MTR-afleiding omdat mogelijk geen drempel in de werking aangenomen kan worden gezien deze positieve in vivo-studie; dit zou bekeken moeten worden i.s.m. Jan van Benthem).

It is proposed to use 3 μg/L as drinking water limit for the present factsheet.

The target value as proposed by the DMR-memorandum is 1 μg/L.

9.11.2 *Surface water for fish consumption*

Fish consumption is relevant because of the classification regarding suspected carcinogenicity.

Input: TL_{hh} = 0.03 mg/kg bw.d, 115 g fish water per day, body weight 70 kg, 10% of TL_{hh} allowed via fish, BCF 0.7 L/kg.
ERL (food) = (0.03 x 0.1 x 70) / 0.115 = 1.8 mg/kg fish.
ERL (water) = 1.8 / 0.7 = 2.6 mg/L.

9.12 Summary and discussion

The existing data indicate that the ecotoxicity of 1,4-dioxane is low. Based on human toxicological data, risk limits of 3 or 30 μg/L are calculated depending on the data and cancer risk level used. New information on human toxicology has recently become available, including evidence for genotoxicity. This may lead to a lower risk limit, probably close to or lower than the DMR-target value. With respect to the monitoring data, there is too little information to derive a 90th percentile concentration in water and data are limited to one location only. Based on the average measured concentration of 0.74 μg/L in 2010 and the drinking water limit value of 3 μg/L, the risk ratio is 0.25. Considering the fact that the 90th percentile will be higher, and the risk limit may be lower, a higher risk ratio may be calculated when more monitoring data become available and human toxicological data are evaluated.

ERL DMR-memorandum	1	μg/L
ERL direct ecotoxicity	57500	μg/L
ERL secondary poisoning	n.r.	μg/L
ERL drinking water	3	μg/L
ERL human fish consumption	2600	μg/L
Environmental concentration	0.74	μg/L
Risk ratio	0.74	ERL DMR
	0.24	ERL DW
	<0.001	ERL ECO/FISH

n.r. = not relevant

9.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- a 90th percentile concentration cannot be established and monitoring data are limited to one location in 2010;
- not relevant for ecology, because the risk ratio is <0.01.

Recommendations

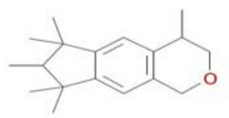
- continue monitoring;
- derive human toxicological risk limits, since these might be critical for water quality standards.

10 Galaxolide (HHCB)

10.1 Introduction

Galaxolide has been put forward by the Waterdienst as a potentially relevant substance because of its widespread use in detergents.

10.2 Chemical identity

Name	Galaxolide
Chemical name	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran
CAS number	1222-05-5
EC number	214-946-9
Molecular formula	$C_{18}H_{26}O$
Molar mass	258.41
Structural formula	
	Sum of isomers with typical composition ≥ 95%
SMILES code	CC1COCC2=CC3=C(C=C12)C(C(C3(C)C)C)(C)C

10.3 Information on uses and emissions

The pourable liquid is used as an ingredient in fragrance oils, by definition of the International Fragrance Association (IFRA) described as fragrance compounds; sometimes in literature also referred to as fragrances, fragrance composition, perfume oil or perfume compositions. HHCB is the largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which HHCB is mixed. Applications of the fragrance oils are in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products, air fresheners et cetera.
Estimated use in the EU was 1307 ton/y in 2004 [58]. The compound is not included in the Pollutant Release and Transfer Register [6].

10.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not Included
Existing Substances Reg. (793/93/EC)	final EU-RAR report available [58]
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	D: Classified as water hazardous class 2 [14]

10.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
EU	4.4	PNEC, EC_{10} *Acartia tonsa* with AF 10	[58]
EU	4.4	PNEC REACH dossier	[8]
D	7		[44]
	1.0	target value for anthropogenous substances without a known specific action	[7]

10.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H400, 410	harmonised classification	[8]
BCF	1584	experimental value	[58]
Human toxicological threshold limit (TL_{hh})	≥ 0.2 mg/kg bw.d	lowest available endpoint from EU-RAR: NOAEL ≥ 20 mg/kg bw.d for F1 rats, F0 exposed from day 14 of pregnancy - day 21 of weaning; AF 100 for intra- and interspecies variation	[58]

10.7 Environmental concentrations

10.7.1 Surface water

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
1994-1996			0.06		0.16	Rhine, n = 32	[58]
			0.08		0.19	Meuse, n = 35	[58]
1995-1996			0.027		0.13	n = 14	[58]
1997	0.006	0.27				n = 5	[58]
2001			0.009*		0.015	n = 8	[58]
2002-2003					0.01*	6 locations, 270 samples	[58]
2003				0.15		66 samples	[59]

* quantification not reliable

10.7.2 STP effluent

Year	Min [µg/L]	Max [µg/L]	Median/mean [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
1995-1996		0.63	0.36		n = 4	[58]
2001		2.2	1.6		n = 4	[58]
2002-2003			1.81	7.35*	n = 15	[58]
2003			10		n = 34	[59]

* quantification not reliable

10.8 Removal upon water treatment

Galaxolide is not proposed by the RIWA as a drinking water relevant compound.

10.9 Environmental risk limits based on direct ecotoxicity

For the present assessment, the EU PNEC of 4.4 µg/L is selected.

10.10 Environmental risk limits based on secondary poisoning

Secondary poisoning is relevant because of the high BCF. In the EU-RAR [58], a $PNEC_{oral}$ of 33.3 and 3.33 mg/kg fd are given.
The higher value is based on the results of a 90-days oral study in rats (NOAEL 150 mg/kg bw.d), using a conversion factor of 20 to calculate the daily dose into a concentration in feed, and an assessment factor of 90. The NOAEL is in fact a ≥-value, so is the $PNEC_{oral}$. Using this value and the BCF of 1584 L/kg, the ERL for secondary poisoning is 33.3 / 1584 = ≥ 21 µg/L.
The $PNEC_{oral}$ of 3.33 is based on a NOAEL of 50 mg/kg bw.d in rats (maternal toxicity in a developmental study), a conversion factor of 20 and an assessment factor of 300. Using this value and the BCF of 1584 L/kg, the ERL for secondary poisoning is 3.33 / 1584 = 2.1 µg/L. The NOAEL for developmental toxicity in this study was 150 mg/kg bw.d. For derivation of ERLs in the framework of INS, preference would be given to the study with the longer test duration, or alternatively use the lower endpoint of 50 mg/kg bw.d with an assessment factor of 90. This would result in an ERL for secondary poisoning of 11 / 1584 = 7 µg/L.

10.11 Environmental risk limits based on human toxicology

10.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = ≥ 0.2 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.2 x 0.1 x 70) / 2 = 0.7 mg/L = ≥ 700 µg/L.

Note that in the EU-RAR the risk assessment for exposure via water is also performed, but starting with a higher NOAEL of ≥ 150 mg/kg bw.d from a repeated dose toxicity study, with an assessment factor of 100. This leads to a human threshold limit of ≥ 1.5 mg/kg bw.d.

For anthropogenic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

10.11.2 Surface water for fish consumption

Human exposure via fish consumption is considered relevant because of the high BCF.
Input: TL_{hh} = ≥ 0.2 mg/kg bw.d, 115 g fish per day, body weight 70 kg; 10% of TL_{hh} allowed via fish consumption, BCF = 1584 L/kg.
ERL (food) = (≥ 0.2 x 0.1 x 70) / 0.115 = ≥ 6.1 mg/kg fish.
ERL (water) = ≥ 6.1 / 1584 = ≥ 3.8 µg/L.

10.12 Summary and discussion

The ecotoxicological data have been evaluated on the European level, and the PNEC for direct ecotoxicity of 4.4 µg/L is considered to be reliable. This also holds for the human toxicological data, although the endpoint refers to a ≥-value. Reliable monitoring data are lacking, the most recent data from the EU-RAR refer to 2003 and reported data are not reliable due to analytical problems. The data reported by [59] also date back to 2003, and only an average is available. Based on the EU PNEC for direct ecotoxicity of 4.4 µg/L and the most recent monitoring data (average 0.15 µg/L in 2003), the risk ratio is 0.03.

ERL DMR-memorandum	1	µg/L
ERL direct ecotoxicity	4.4	µg/L
ERL secondary poisoning	7	µg/L
ERL drinking water	≥ 700	µg/L
ERL human fish consumption	≥ 3.8	µg/L
Environmental concentration		µg/L
Risk ratio		

10.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA; relevance for drinking water and ecology cannot be assessed because recent reliable monitoring data are lacking; the risk limit for ecology is relatively low.

Recommendation

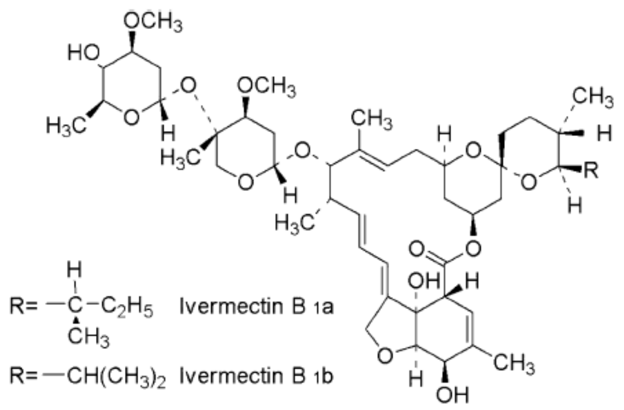
- continue monitoring.

11 Ivermectin

11.1 Introduction

Ivermectin is put forward by the Waterdienst as a potential relevant compound because of its widespread use in human and veterinary medicine and high ecotoxicity to water organisms.

11.2 Chemical identity

Name	ivermectin
Chemical name	Ivermectin (22,23-dihydroavermectin B1a + 22,23-dihydroavermectin B1b)
CAS number	70288-86-7 (70161-11-4 + 70209-81-3)
EC number	274-536-0
Molecular formula	C48H74O14 (22,23-dihydroavermectin B1a) + C47H72O14 (22,23-dihydroavermectin B1b)C12H17NO
Molar mass	875.11
Structural formula	
SMILES code	O[C@@]12[C@]3([H])C(O[C@@](C[C@]5(CC[C@H](C)[C@]([C@@H](C)CC)([H])O5)O4)([H])C[C@@]4([H])C/C=C(C)/[C@@H](O[C@]6([H])O[C@@H](C)[C@H](O[C@@]7([H])C[C@H](OC)[C@@H](O)[C@H](C)O7)[C@@H](OC)C6)[C@@H](C)/C=C/C=C1\CO[C@@]([H])2[C@H](O)C(C)=C3)=O

11.3 Information on uses and emissions

Ivermectin is mainly used as a veterinary drug, against parasites. It belongs to the family of avermectins, which are macrocyclic lactones isolated from the soil actinomycete Streptomyces avermitilis. It is also applied as human pharmaceutical, one product is registered in the Netherlands [4], but data on use are not available [5]. Liebig et al. [60] refer to a publication of 2002 which states that over 5 billion doses have been sold worldwide since the introduction in the 1980s. For an inventory on the potential risks of veterinary drugs for surface water [61], data on the use of individual compounds in the Netherlands could not be retrieved. The compound is not included in the Pollutant Release and Transfer Register [6].

11.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not included
Biocides (98/8/EC)	Not included
PBT substances	Not investigated; not applicable
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	registered as veterinary drug

11.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [μg/L]	Remark	Reference
NL	-		
	3×10^{-8}	PNEC, NOEC *Daphnia magna* 0.0003 ng/L with AF 10	[60]*
	0.1	target value for biologically active compounds in surface water for abstraction of drinking water	[7]

* carried out by experts from wide range of countries

11.6 Physico-chemical properties, fate and distribution

The following input data were used by Liebig et al. (2010) for PEC calculations.

Parameter	Unit	Value	Remark	Reference
Water solubility	[mg/L]	2.0-4.1		[60]
pK_a			neutral at all pH values	
log K_{ow}		3.2	measured	
Vapour pressure	[Pa]	$<1.9 \times 10^{-9}$	measured	
Henry's law constant	[-]	4.8×10^{-26}	estimated	
log K_{oc}	log [L/kg]	3.6-4.4	measured	
Hydrolysis half-life	DT_{50} [d]			
Photolysis half-life	DT_{50} [d]			
Biodegradation in water/sediment systems	DT_{50} [d]	30 130	degradation water degradation sediment	

11.7 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H300, 311, 319, 361, 373, 400, 410	notified classification	[8]
BCF	105 L/kg	estimated value	[17]
Human toxicological threshold limit (TL_{hh})	0.001 mg/kg bw		[62]

11.8 Environmental concentrations

11.8.1 Netherlands

Ivermectin was not included in the 2002-screening for human and veterinary drugs by the former RIZA, in the absence of an adequate analysis method [33].

11.8.2 Other information

Ivermectin was not found in surface water in the UK [63], it was detected in sediment at a maximum of 4.9 μg/kg at an outdoor cattle site. According to [61], presence of ivermectin in the water phase is not expected due to its relatively high sorption coefficient.

Fernández et al. [64] report measured concentrations of ivermectin in water of 0.006-0.118 ng/L in a semi-field study into the emissions due to run-off of dung-treated land in Spain.

Several estimates of concentrations in surface water are available, values depend on the models and scenarios used. Estimated initial concentrations range from 20 to 35 ng/L [60,61,65]. In a higher tier assessment, the highest PEC is estimated as 12.9 ng/L [60]. Time weighted average concentrations up to 5.1 µg/L are reported in [63], while a 21-days time weighted average PEC of 0.7 ng/L is calculated in [60]. In the PEC-calculations, direct emissions to surface water, i.e. excretion by cattle standing in shallow waters, is the most critical route [60,61].

11.9 Removal upon water treatment

Ivermectine is not proposed by the RIWA as a drinking water relevant compound.

11.10 Environmental risk limits based on ecotoxicity

A PNEC of 0.00003 ng/L (0.03 pg/L) is proposed [60] based on a reproduction study with *Daphnia magna* (NOEC 0.3 pg/L, AF 10). The laboratory study with 21-days continuous exposure represents a worst case as compared to field conditions, since due to sorption ivermectin will only be present in the water phase during short periods of time. However, short-term peak concentrations still induce effects, as was shown in the mesocosm study effects on ecosystem structure and function were obsserved in a model ecosystem after 4 repeated daily doses of 30 ng/L nominal, despite the dissipation half-life in water of 3-5 days [66]. The initial measured concentrations in this study were circa 19 ng/L, the NOEC from this study is thus <19 ng/L. A PNEC cannot be derived, because effects were seen at the lowest test concentration.

11.11 Environmental risk limits based on secondary poisoning

Although the estimated BCF is around the trigger of 100 L/kg, this route is not considered relevant since vertebrates are not likely to be more sensitive than arthropods.

11.12 Environmental risk limits based on human toxicology

11.12.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.001 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.001 x 0.1 x 70) / 2 = 0.0035 mg/L = 3.5 µg/L.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

11.12.2 Surface water for fish consumption

Probably relevant because of H361 (notified classification).

Input: TL_{hh} = 0.001 mg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 105 L/kg.
ERL (food) = (0.001 x 0.1 x 70) / 0.115 = 0.061 mg/kg fish.
ERL (water) = 0.061 / 105 = 0.58 µg/L.

11.13 Summary and discussion

The data on the ecotoxicological effects of ivermectin are considered to be reliable. Based on the laboratory studies, an ERL of 0.03 pg/L is obtained. The exposure levels in the mesocosm study were much higher, but effects were seen at the lowest level tested. Based on realistic worst case PECs in surface water of

0.7 to 12.9 ng/L and PNEC of 0.0003 ng/L, PEC/PNEC ratios of 2.3×10^4 to 4.3×10^5 are reported [60].
The estimated PECs probably represent a scenario that is not generally valid for the Netherlands, i.e. direct emission to shallow waters, although at some places this may occur. The main issue is that there are no monitoring data on ivermectin in water to validate the PECs. The data from Boxall et al. [63] confirm the assumption of Jongbloed et al. [61] that sorption will lead to rapid dissipation from the water phase. It is realised, however, that short-term peaks may induce effects. At the same time, analytical techniques that allow for monitoring at the level of the PNEC are not available, and the chance of detecting peaks is quite small. For this compound, alternative monitoring methods such as passive sampling might be an option to determine whether or not exposure occurs at ecologically relevant concentrations.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.00003	ng/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	3.5	µg/L
ERL human fish consumption	0.58	µg/L
Environmental concentration	?	µg/L
Risk ratio		ECO
		DMR

n.r. = not relevant

11.14 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and the compound has not been detected;
- potentially relevant for ecology due to short-term peaks, but the chance of detecting those peaks during normal monitoring is limited.

Recommendation

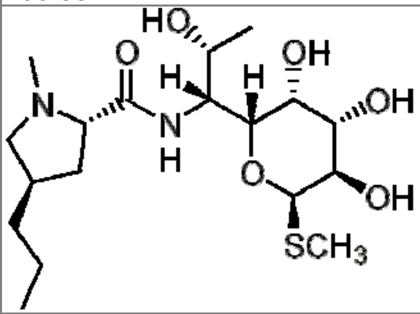
- investigate options for alternative monitoring approaches.

12 Lincomycin

12.1 Introduction

Lincomycin is put forward by the RIWA as a drinking water relevant compound because it is toxicologically relevant and is detected in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may give rise to public concern, and the potential development of resistance to antibiotics is seen as an important issue by drinking water experts. The risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

12.2 Chemical identity

Name	Lincomycin
Chemical name	(2S,4R)-N-[(1R,2R)-2-hydroxy-1-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(methylsulfanyl)oxan-2-yl]propyl]-1-methyl-4-propylpyrrolidine-2-carboxamide
CAS number	154-21-2
EC number	205-824-6
Molecular formula	C18H34N2O6S
Molar mass	406.55
Structural formula	
SMILES code	CCCC1CC(N(C)C1)C(=O)NC(C(C)O)C2OC(SC)C(O)C(O)C2O

12.3 Information on uses and emissions

Lincomycin (as lincomycin hydrochloride) is registered as a veterinary pharmaceutical and can be used as an antibiotic for dogs, cats, poultry, cows, sheep and pigs. A total of 13 products is registered in the Netherlands [4]. Use data are not available, the compound is not included in the Pollutant Release and Transfer Register [6].

12.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as veterinary pharmaceutical in NL

12.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

12.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	-	not included in ESIS or C&L inventory	[8,9]
log K_{ow}	0.4		[67]
	0.2	experimental EpiSuite	[1]
BCF	<100 L/kg	Estimated using log K_{OW}	[17]
Human toxicological threshold limit (TL_{hh})	0.6 mg/person	EMEA; based on 10 µg/kg bw	[11]
	0-0.03 mg/kg bw	JECFA	[68]

12.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2006	<	<	<		4 (Brakel)	[12]
	<	<	<	<	13 (Nieuwegein)	
	<	0.01	<	<	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2007	<	<	<		4 (Brakel)	[12]
	<	<	<	<	13 (Nieuwegein)	
	<	<	<	<	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2008	<	<	<		4 (Brakel)	[12]
	<	<	<		9 (Keizersveer)	
	<	<	<	<	13 (Nieuwegein)	
	<	0.01	<	<	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2009	<	<	<		1 (Heel)	[12]
	<	<	<		4 (Brakel)	
	<	<	<	<	15 (Keizersveer)	
	<	<	<	<	13 (Nieuwegein)	
	<	0.01	<	<	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2010	<	<	<	<	13 (Brakel)	[12]
	<	<	<	<	13 (Keizersveer)	
	<	<	<	<	13 (Nieuwegein)	
	<	0.02	<	0.014	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
	<	<	<	<	12 (Stellendam)	

In 2005 and 2006, lincomycin was not present in drinking water and sources for drinking water abstraction [11].

The HWL has detected lincomycin several times during monitoring in 2010-2011 (Astrid Fischer, HWL, pers. comm.).

In 2010, lincomycin was not detected in the influent and effluent of an STP by Water board Rijnland.

12.8 Removal upon water treatment

Based on a log K_{ow} of 1.37, VP of 3.57E-15 and BIOWIN3 value of 1.6871 (months to recalcitrant), lincomycin is considered difficult to remove by simple surface water treatment. However 40-80% can be removed by powdered activated carbon (PAC) or granular activated carbon (GAC). Reduction of the level of purification treatment will therefore not be possible.

12.9 Environmental risk limits based on direct ecotoxicity

No regulatory standard or reliable proposal is available. The following ecotoxicity data are available:

Taxon	Species	L/EC_{50} Value [mg/L]	Remark	Reference
Bacteria	*Vibrio fischeri*	> 100	30 min.	[69]
Cyanophyta	*Anabaena flos-aquae*	0.0305	72 h	[67]
Algae	*Pseudokirchneriella subcapitata*	0.070	72 h	[69,70]
Rotifera	*Brachionus calyciflorus*	25	48 h mortality	[69]
	Brachionus calyciflorus	0.68	48 h population growth rate	[69]
Crustacea	*Artemia sp.*	283	48 h	[39]
	Ceriodaphnia dubia	14	48 h mortality	[69]
	Ceriodaphnia dubia	7.2	48 h population growth rate	[69]
	Daphnia magna	> 900	48 h	[67]
	Daphnia magna	379		[39]
	Tamnocephalus platyurus	30	24 h	[69]
Fish	*Danio rerio*	> 1000	96 h	[69]
	Lepomis macrochirus	> 980	96 h	[67]
	Oncorhynchus mykiss	> 980	96 h	[67]

The >-values cannot be used for derivation of an ERL. However, the data indicate that fish are not sensitive towards lincomycin, and the base set is considered complete. The 48-hours test with *Brachionus calyciflorus* is considered chronic in view of its short life cycle. Because only L/EC_{50}-values are available, an ERL may be derived using an assessment factor of 1000 on the lowest EC_{50}, resulting in an ERL for direct ecotoxicity of 0.03 µg/L. Based on the available information, algae and rotifers seem to be relatively sensitive, whereas other aquatic organisms are not. This is consistent with the mode of action. It can be argued that in this case, an assessment factor of 100 on the acute endpoint for algae might be protective, leading to an ERL of 0.3 µg/L.

12.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

12.11 Environmental risk limits based on human toxicology

12.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.6 mg person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since the TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (0.6 x 0.1) / 2 = 0.03 mg/L = 30 µg/L.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

12.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

12.12 Summary and discussion

Based on the available ecotoxicity data, an ERL of 0.03 µg/L may be derived. This value is derived using a high assessment factor, since only L/EC_{50}-data are available. It can be argued that in view of the mode of action, an assessment factor of 100 on the acute endpoint for algae might be protective, leading to an ERL of 0.3 µg/L. The TL_{hh} is also relatively low, leading to a drinking water limit of 30 µg/L, although this value is much higher than the target value as proposed by the drinking water companies of 0.1 µg/L.
The compound is found at Nieuwersluis in concentrations of 0.01 to 0.02 µg/L, which is below the DMR-target value and the ERL for direct ecotoxicity. However, data from recent screening monitoring indicate the presence of lincomycin in drinking water sources. The ERL of 0.3 µg/L is relatively low, if concentrations increase the compound might be relevant for ecosystems.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.3	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	30	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.01	µg/L
Risk ratio	0.1	ERL DMR
	<0.001	ERL DW
	0.03	ERL ECO

n.r. = not relevant

12.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- a 90th percentile concentration cannot be established and the compound is detected at one location only above the limit of quantification (LOQ);
- potentially relevant for ecology, because the risk ratio is > 0.01, but the compound is detected at one location only.

Recommendation

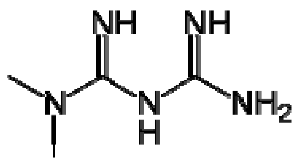
- continue monitoring.

13 Metformin

13.1 Introduction

Metformin is put forward by the RIWA as a drinking water relevant compound because it is toxicologically relevant and frequently present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may give rise to public concern, and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

13.2 Chemical identity

Name	Metformin
Chemical name	N,N-dimethylimidodicarbonimidic diamide
CAS number	657-24-9
EC number	211-517-8
Molecular formula	$C_4H_{11}N_5$
Molar mass	129.2
Structural formula	
SMILES code	N=C(N)NC(=N)N(C)C

13.3 Information on uses and emissions

Metformin is registered as a human pharmaceutical in the EU and the Netherlands. Metformin has been on the market since 1967 and is primarily used for type 2 diabetes. In the Netherlands, 92 products are registered [4]. The estimated number of users was 42,6870 in 2006 and has increased to over 500,000 in 2010 [5]. In 2007, the estimated use of metformin hydrochloride was 207,190 kg, while the use is expected to increase to 256,103 kg in 2020 [23]. The compound is not included in the Pollutant Release and Transfer Register [6].

13.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not applicable
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human pharmaceutical in NL

13.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
	64	PNEC, EC_{50} *Daphnia* with AF 1000	[28]
	64	PNEC, EC_{50} *Daphnia* with AF 1000	[70]
	101	PNEC, background not known	[27]
	≥ 240	indicative PNEC, NOEC cyanobacteria with AF 50	[29]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

13.6 Classification, secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302	notified classification	[8]
log K_{ow}	-2.6		[28]
BCF	<100	Estimated using log K_{OW}	[17]
Human toxicological threshold limit (TL_{hh})	not available		

13.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
2010	0.41	0.68	0.56		6 (Brakel)	[12]
	0.24	0.87	0.457		6 (Nieuwegein)	
	0.24	0.54	0.347		6 (Nieuwersluis)	
	0.14	0.57	0.348		6 (Andijk)	

A 90^{th} percentile value is not available, but considering the fact that the difference between minimum and maximum values is relatively small, the overall average over 2010 of 0.43 µg/L is considered a good estimate.

In a research monitoring project with passive samplers, Van der Oost and Nguyen [34] did not detect metformin.

13.8 Removal upon water treatment

Based on a log Kow of -2.64, VP of 7.88E-05 and BIOWIN3 value of 2.9137 (weeks to months), metformin is considered difficult to remove by the current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

13.9 Environmental risk limits based on direct ecotoxicity

On the Swedish FASS website [28], as well as in France [70] a PNEC of 64 µg/L is proposed, based on the lowest EC_{50} of 64 mg/L for *Daphnia magna* [71]. No effects are reported in chronic studies with fish and cyanobacteria at concentrations of ≥ 32 and ≥ 12 mg/L, respectively. Therefore, Van der Aa et al. (2011) propose an indicative PNEC of ≥ 240 µg/L based on the ≥-NOEC for cyanobacteria with an assessment factor of 50 [29]. In Norway, a PNEC of 101 µg/L is proposed [27], but in the same report also a value of 20 µg/L is mentioned. The background of both values is unclear. For the purpose of this project, a PNEC of 64 µg/L is used since this *D. magna* appears to be more sensitive than fish and algae or cyanophyta, and no proper chronic NOECs are available.

13.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

13.11 Environmental risk limits based on human toxicology

13.11.1 Surface water for drinking water abstraction

A human toxicological threshold limit is not available. The recommended starting dose for adults is two to three times 500 mg (1000-1500 mg/day), the maximum dose is three times 1000 mg [4]. For other pharmaceuticals, the lowest therapeutic dose with an assessment factor of 100 was used to establish a provisional ADI [11]. For metformin this would lead to a value of 10 mg per person per day.

Input: TL_{hh} = 10 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since the TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (10 x 0.1) / 2 = 0.5 mg/L = 500 µg/L.
If metformin is put forward for further actions , this information should be checked by experts.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

13.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

13.12 Summary and discussion

The PNEC for direct ecotoxicity as proposed in France and Sweden is derived using a high assessment factor, since no unbound chronic data are available. Based on the available information, aquatic organisms seem to be relatively insensitive. Based on the ERL of 64 µg/L and the overall average concentration in 2010 of 0.43 µg/L, the risk ratio is 0.007. Thus, from an ecotoxicogical point of view, the compound is not specifically relevant. The therapeutic dose is also quite high, indicating that a drinking water limit based on human toxicological data may be much higher than the target value of 0.1 µg/L as proposed by the drinking water companies. However, it was identified as one of the drugs for which annual consumption shows a steady increase. This is confirmed by monitoring data which show the presence in surface water at a level of about 0.4 to 0.5 µg/L. It should also be noted that minimum and maximum levels are relatively close to each other, indicating a long-term presence instead of incidental peaks. Monitoring data are restricted to four locations only. Using the target value of 0.1 µg/L as proposed in the DMR-memorandum, the risk ratio is 4.3. Using the drinking water limit based on human toxicological data, the risk ratio is 0.001.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	64-240	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	500	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.43	µg/L
Risk ratio	4.3	ERL DMR
	0.001	ERL DW
	0.007	ERL ECO

n.r. = not relevant

13.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90^{th} percentile concentrations are higher than the DMR-target value, human-toxicological risk limit most likely >> DMR-target value; however, monitoring data indicate that the compound is present at constant concentrations rather than incidental high peaks;
- not relevant for ecology, because the risk ratio is <0.01.

Recommendation

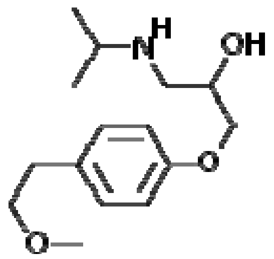
- continue and expand monitoring.

14 Metoprolol

14.1 Introduction

Metoprolol is proposed by the RIWA as a drinking water relevant compound, because it is frequently present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may give rise to public concern, and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

14.2 Chemical identity

Name	metoprolol
Chemical name	1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol
CAS number	37350-58-6
EC number	253-483-7
Molecular formula	C15H25NO3
Molar mass	267.37
Structural formula	
SMILES code	COCCc1ccc(OCC(O)CNC(C)C)cc1

14.3 Information on uses and emissions

Metoprolol is a selective β1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure (http://www.drugbank.ca/drugs/DB00264). The active substance metoprolol is employed either as metoprolol succinate or metoprolol tartrate (where 100 mg metoprolol tartrate corresponds to 95 mg metoprolol succinate), respectively as prolonged-release or conventional-release formulation. In the Netherlands, 74 products containing metoprolol are registered [4]. The estimated number of users in the Netherlands has increased from about 800,000 in 2006 to almost 975,000 in 2010 [5]. The estimated use of metoprolol was 22,681 kg in 2007, while the use is expected to increase to 28,061 kg in 2020 [29]. The compound is not included in the Pollutant Release and Transfer Register [6].

14.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human pharmaceutical in NL

14.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
CH	64; 0.5	AA-EQS, based on direct ecotoxicity; see comments under section 14.9	[72]
CH	76	MAC-EQS, based on direct ecotoxicity	[72]
S	58.3	PNEC, industry MSDS	[28]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

14.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	R 20/22, R36, R52/53	industry data	[16]
	H302, 315, 319, 332, 335, 361	notified classification	[8]
log K_{ow}	1.88	experimental value	[1]
BCF	7.9	estimated, log K_{ow} 1.88	[17]
Human toxicological threshold limit (TL_{hh})	1 mg/person	provisional ADI	[11]

14.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2005	0.03	0.06				autumn 2005	[11]
2006		0.2				114 measurements; RIWA data	[10]
2006	0.02	0.04				spring 2006	[11]
2006	<	0.18	0.065	0.0754	0.159	12 (Nieuwegein)	[12]
	0.06	0.2	0.105	0.118	0.2	12 (Nieuwersluis)	
	<	0.1	<	0.0164	0.086	11 (Andijk)	
2007	0.014	0.038	0.0235	0.0238	0.0362	12 (Lobith)	[12]
	<	0.11	0.08	0.0619	0.102	13 (Nieuwegein)	
	<	0.14	0.11	0.0892	0.136	13 (Nieuwersluis)	
	<	0.06	<	0.0185	0.06	13 (Andijk)	
2008	<	<	*	<	*	7 (Liège)	[12]
	<	0.068	*	0.037	*	4 (Heel)	
	<	0.04	*	0.0287	*	4 (Brakel)	
	0.035	0.13	*	0.08	*	9 (Keizersveer)	
	0.011	0.047	0.027	0.0278	0.045	13 (Lobith)	
	<	0.13	0.09	0.0775	0.124	12 (Nieuwegein)	
	0.1	0.18	0.13	0.141	0.18	11 (Nieuwersluis)	
	<	0.06	<	0.0225	0.059	10 (Andijk)	
2009	0.03	0.11	*	0.065	*	4 (Brakel)	[12]
	<	0.21	<	<	0.174	15 (Keizersveer)	
	0.039	0.12	0.059	0.0673	0.12	13 (Lobith)	
	<	0.13	0.09	0.0823	0.126	11 (Nieuwegein)	
	0.11	0.25	0.16	0.159	0.238	11 (Nieuwersluis)	
	<	0.12	0.0175	0.0365	0.12	10 (Andijk)	
2010	<	<	*	<	*	4 (Namêche)	[12]
	<	<	*	<	*	4 (Liège)	
	<	0.07	<	<	0.07	13 (Brakel)	
	0.04	0.19	0.12	0.114	0.182	13 (Keizersveer)	
	0.053	0.14	0.071	0.0773	0.124	12 (Lobith)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
	<	0.13	<	0.0517	0.118	13 (Nieuwegein)	
	0.014	0.19	0.11	0.094	0.186	13 (Nieuwersluis)	
	<	0.09	<	<	0.078	13 (Andijk)	
	<	0.1	0.07	0.07	0.1	12 (Stellendam)	

The overall average of the 90^{th} percentile concentration in Dutch sampling points of the RIWA over 2010 is 0.12 µg/L.

In 2008, the Water board De Dommel sampled nine locations, concentrations of metropolol ranged from 0.14 to 1.1 µg/L. This is higher than the values reported by the RIWA.

Water board Roer and Overmaas provided monitoring data for the River Roer in 2008 and 2009. In 2008, concentrations ranged from 0.11 to 0.51 µg/L (10 samples, 90^{th} percentile 0.47 µg/L). In 2009, concentrations ranged from 0.22 to 0.36 µg/L (4 samples, 90^{th} percentile 0.28 µg/L). These concentrations are also higher than reported by the RIWA.

Rademaker and De Lange [31] summarised monitoring data of pharmaceuticals in the Netherlands, based on an unpublished study by Verstraaten [32], the RIWA reports from 2003, 2004 and 2005 and a RIZA report from 2003 [33]. Metopolol was found in 59 out of 120 samples (49%), the highest concentration was 0.42 µg/L, the average was 0.023 µg/L.

Versteegh et al. [11] report concentrations in STP effluent of 0.32 µg/L in autumn 2005, and 0.27 µg/L in spring 2006 (one sampling point).

According to data from the Waterdienst, metoprolol is very often found in STPs. Concentrations range from 0.28 to 4 µg/L, the median is 1.3 µg/L, the 90th percentile is 2.4 µg/L (Waterdienst data).

14.8 Removal upon water treatment

Based on a log Kow of 1.88, VP of 2.88E-07 and BIOWIN3 value of 2.6511 (weeks to months), metoprolol is considered difficult to remove by the current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

14.9 Environmental risk limits based on direct ecotoxicity

The draft AA-EQS of 64 µg/L proposed by Switzerland is based on a chronic NOEC for *Daphnia magna* of 3.2 mg/L with an assessment factor of 50. There is also a chronic study in fish, in which effects on gill structure are observed. The NOEC of this study is 5 µg/L, but questions have been raised as to whether this endpoint is relevant for derivation of water quality standards. Using this lower endpoint, the AA-EQS may be adapted to 0.5 µg/L. For the present assessment, the lower value is considered, since for a national evaluation these effects on gills would most likely be considered as a relevant endpoint.

14.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

14.11 Environmental risk limits based on human toxicology

14.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 1 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (1 x 0.1) / 2 = 0.05 mg/L = 50 µg/L.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

14.11.2 Surface water for fish consumption

Probably relevant because of H361 (notified classification).

Input: TL_{hh} = 1 mg person, 115 g fish per day, 10% of TL_{hh} allowed via fish consumption, BCF = 7.9 L/kg. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (food) = (1 x 0.1) / 0.115 = 0.87 mg/kg fish.
ERL (water) = 0.87 / 7.9 = 0.11 mg/L.

14.12 Summary and discussion

The ERLs for direct ecotoxicity as proposed in Switzerland are based on a thorough literature survey performed by known experts. Discussions have been raised, however, on the relevance of effects on gill structure for risk limit derivation and the higher value of 64 µg/L is chosen by the Swiss experts. In contrast, RIVM would most likely advise to use the lower value of 0.5 µg/L.
There are no human toxicological data, the provisional drinking water limit has been derived from the lowest effective dose, which results in a value that is much higher than the target value as proposed by the drinking water companies of 0.1 µg/L.
The monitoring dataset is quite extensive. At some sampling stations, metoprolol is not detected at concentrations higher than the reporting limit of 0.1 µg/L, which is equal to the DMR-target value. The average of 90^{th} percentile values over 2010 is 0.12 µg/L. It should be noted that higher concentrations may be found in smaller water bodies, as indicated by the data from the Dommel area in 2011 and River Roer in 2008 and 2009.
The 90^{th} percentile of concentrations in STP-effluents is 1.3 µg/L. Assuming a dilution factor of 10, concurrent estimated concentrations in surface water are 0.13 µg/L, which is in accordance with measured data.
Based on the chronic ERL of 0.5 µg/L for direct ecotoxicity and the overall average of 90^{th} percentile concentrations in 2010 of 0.12 µg/L, the risk ratio is 0.24. Using the target value of 0.1 µg/L as proposed in the DMR-memorandum, the risk ratio is 1.2. Using the drinking water limit based on human toxicological data, the risk ratio is 0.002.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.5	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	50	µg/L
ERL human fish consumption	110	µg/L
Environmental concentration	0.12	µg/L
Risk ratio	1.2	ERL DMR
	0.002	ERL DW
	0.24	ERL ECO

n.r. = not relevant

14.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90^{th} percentile concentrations are higher than the DMR-target value at multiple locations and time points and data from water boards suggest that concentrations in smaller water bodies may be higher; concentrations may increase due to increased use; the human-toxicological risk limit is relatively low;
- relevant for ecology, because the risk ratio is > 0.1.

Recommendations

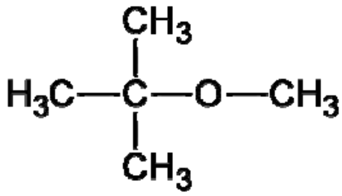
- consider BKMW or Regeling monitoring KRW;
- continue monitoring;
- evaluate key-study for ecological risk limit.

15 MTBE

15.1 Introduction

MTBE (Methyl tertiair-Butyl Ether) is proposed by the RIWA as a drinking water relevant compound, because it is frequently present in surface water used for drinking water abstraction. Furthermore, the compound has a low odour threshold. The presence of this compound in drinking water is seen as damaging to the reputation of the drinking water companies.

15.2 Chemical identity

Name	MTBE
Chemical name	propane, 2-methoxy-2-methyl-
CAS number	1634-04-4
EC number	216-653-1
Molecular formula	C5H12O
Molar mass	88.15
Structural formula	
SMILES code	CC(C)(C)OC

15.3 Information on uses and emissions

MTBE has been produced in the Netherlands since 1984. Since 1988 it has been used on a large scale to replace lead as fuel additive to raise the octane number. Emission sources are amongst others petrol stations and commercial shipping [73].

15.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	final EU-RAR report available [74]
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	

15.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [mg/L]	Remark	Reference
NL	2.6	MPC for direct ecotoxicity	[75]
EC	2.6	PNEC, based on NOEC Americamysis bahia, AF 10	[74]
EU	2.1	PNEC, probably based on QSAR	[8]
EU	5.1	PNEC, based on NOEC *Daphnia magna*, AF 10	[8]
	1	target value for anthropogenic compounds in surface water for abstraction of drinking water	[7]

15.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H315	harmonised classification	[8]
log K_{ow}	1.06		[74]
	0.94		[1]
BCF	1.5 L/kg	experimental	[74]
Human toxicological threshold limit (TL_{hh})	0.3 mg/kg bw.d		[75]

15.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark n (location)	Reference
2006	<	0.53	0.08	0.179	0.526	13 (Eijsden)	[12]
	<	4.4	1.7	1.84	3.06	153 (Heel)	
	0.05	2.3	0.18	0.432	1.86	13 (Brakel)	
	<	2.7	0.24	0.605	1.9	54 (Keizersveer)	
	0.056	4.01	0.261	0.405	0.802	363 (Lobith)	
	0.07	2.2	0.27	0.533	1.59	26 (Nieuwegein)	
	0.05	0.7	0.24	0.304	0.7	13 (Nieuwersluis)	
	<	0.02	<	<	0.02	12 (Andijk)	
	<	0.19	0.045	0.0654	0.187	12 (Stellendam)	
2007	<	<	<	<	<	10 (Liège)	[12]
	<	0.51	0.07	0.124	0.414	13 (Eijsden)	
	<	3.2	1.4	1.31	1.7	149 (Heel)	
	<	1	0.12	0.265	0.84	13 (Brakel)	
	0.084	3	0.31	0.533	1.2	51 (Keizersveer)	
	0.0246	5.56	0.137	0.21	0.337	365 (Lobith)	
	<	0.415	0.0714	0.0939	0.198	28 (Nieuwegein)	
	<	0.177	0.0766	0.0935	0.173	12 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.22	0.068	0.0721	0.114	25 (Stellendam)	
2008	<	<	<	<	<	12 (Liège)	[12]
	0.02	0.22	0.06	0.0915	0.22	13 (Eijsden)	
	<	1	0.16	0.246	0.764	13 (Heel)	
	<	0.9	<	0.186	0.84	12 (Brakel)	
	<	1.5	0.19	0.253	0.604	53 (Keizersveer)	
	0.0444	1.65	0.115	0.147	0.221	352 (Lobith)	
	0.05	6	0.1	0.703	3.69	16 (Nieuwegein)	
	<	0.46	0.06	0.0962	0.348	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.11	0.02	0.0321	0.101	12 (Stellendam)	
2009	<	<	<	<	<	13 (Liège)	[12]
	0.01	0.61	0.08	0.125	0.478	13 (Eijsden)	
	<	0.8	<	0.175	0.76	13 (Brakel)	
	0.04	0.91	0.16	0.224	0.464	52 (Keizersveer)	
	<	5.12	0.0882	0.157	0.19	344 (Lobith)	
	<	0.5	0.09	0.148	0.448	13 (Nieuwegein)	
	<	0.18	0.07	0.0892	0.18	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.08	0.02	0.0292	0.076	13 (Stellendam)	
2010	<	0.25	*	<	*	7 (Namêche)	[12]
	<	<	*	<	*	9 (Liège)	
	<	0.56	0.02	0.0788	0.384	13 (Eijsden)	
	<	0.34	0.13	0.137	0.32	13 (Heel)	
	<	0.35	<	0.0919	0.306	13 (Brakel)	
	<	0.66	0.0755	0.129	0.29	50 (Keizersveer)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark n (location)	Reference
	<	13	0.082	0.226	0.31	186 (Lobith)	
	<	0.22	0.05	0.0708	0.208	13 (Nieuwegein)	
	<	0.6	0.08	0.136	0.54	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
	<	0.05	0.02	0.0192	0.05	13 (Stellendam)	

Concentrations at Andijk and Stellendam are much lower than at the other locations. Without Andijk and Stellendam, the overall average of the 90th percentile in 2010 is 0.34 µg/L. According to the RIWA [50] the frequency and intensity of detections at Lobith in 2010 show a decreasing trend as compared to those in 2009. When sampling frequency is high, incidental peaks may be found, as shown by the maximum value of 13 µg/L which was detected at Lobith on November 21, 2010. This peak concentration is close to the odour threshold limit (see section 15.11.1).

During screening monitoring in 2010, MTBE was not detected by the Water board Hollandse Delta (Province of South-Holland) above the reporting limit of 0.01 µg/L (one location, single sampling date).

15.8 Removal upon water treatment

Based on a log Kow of 0.94, VP of 250 mm Hg and BIOWIN3 value of 2.7836 (weeks to months), MTBE is considered difficult to remove by simple surface water treatment.

15.9 Environmental risk limits based on direct ecotoxicity

The PNEC for direct ecotoxicity of 2.6 mg/L from the EU-RAR [74] has been adopted by RIVM as $MPC_{eco,\ water}$ [75] and is also used for the present assessment.

15.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

15.11 Environmental risk limits based on human toxicology

15.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.3 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.3 x 0.1 x 70) / 2 = 1 mg/L = 1000 µg/L.

Swartjes et al. [75] present a drinking water limit of 9420 µg/L, based on the above reported human threshold limit of 0.3 mg/kg bw per day and assuming that an adult of 70 kg drinks 2 L water per day for 64 years, and a child of 15 kg drinks 1.5 L water per day for 6 years. This approach differs from that of the WFD-methodology presented above.

Drinking water limits for odour and taste are 15 and 40 µg/L, respectively [74,75].

The proposed target value for anthropogenic chemicals according to the DMR-memorandum is 1 µg/L.

15.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

15.12 Summary and discussion

An established PNEC for direct ecotoxicity of 2.6 mg/L is available from the EU-RAR. A drinking water limit of 1 mg/L has been derived based on human toxicological data. This value is much higher than the target value as proposed by the drinking water companies of 1 μg/L. The use of a lower drinking water limit is consistent with the reported limits for odour and taste of 15 and 40 μg/L, respectively. The monitoring dataset is quite extensive. At sampling stations Andijk and Stellendam, MTBE is not detected at concentrations higher than the reporting limit (0.01 μg/L) or at low concentrations only. The average of 90th percentile values over 2010 of the other locations is 0.34 μg/L. Concentrations in the Rhine at Lobith tend to decrease as compared to previous years, but peaks far above the DMR-target value and approaching the odour threshold limit were detected upon frequent sampling. Based on the chronic ERL of 2600 μg/L and the overall average of 90^{th} percentile concentrations in 2010 of 0.34 μg/L, the risk ratio is 0.0001. Using the target value of 1 μg/L as proposed in the DMR-memorandum, the risk ratio is 0.34.

ERL DMR-memorandum	1	μg/L
ERL direct ecotoxicity	2600	μg/L
ERL secondary poisoning	n.r.	μg/L
ERL drinking water	15 (odour)	μg/L
ERL human fish consumption	n.r.	μg/L
Environmental concentration	0.34	μg/L
Risk ratio	0.34	ERL DMR
	0.02	ERL DW
	0.0001	ERL ECO

n.r. = not relevant

15.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- MTBE is detected at ≥ 2 locations during multiple years, 90^{th} percentile concentrations are lower than the DMR-target value during the last three years; odour threshold in line with DMR-target;
- not relevant for ecology, because the risk ratio is <0.01.

Recommendations

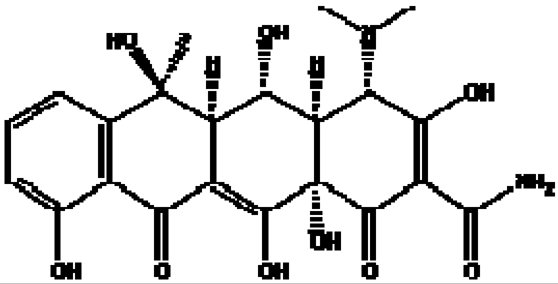
- consider relationship with policy on diffuse sources (VROM, 2007);
- continue monitoring.

16 Oxytetracycline

16.1 Introduction

Oxytetracycline is proposed by the Waterdienst as a potentially relevant compound because of its widespread use as antibiotic.

16.2 Chemical identity

Name	oxytetracycline
Chemical name	4S,4aR,5S,5aR,6S,12aS) -4-(dimethylamino)-3,5,6,10,11,12a-hexahydroxy -6-methyl-1,12-dioxo-1,4,4a,5,5a,6,12,12a-octahydrotetracene -2-carboxamide
CAS number	79-57-2
EC number	201-212-8
Molecular formula	$C_{22}H_{24}N_2O_9$
Molar mass	460.434
Structural formula	oxytetracycline 
SMILES code	O=C(N)C(=C(O)C(N(C)C)C(C1(O)C(O)=C(C2C(O)(c(c3c(O)cc4)c4)C)C3(=O)C2O)C1(=O)

16.3 Information on uses and emissions

Oxytetracycline is a broad spectrum antibiotic that is active against a wide variety of bacteria. However, some strains of bacteria have developed resistance to this antibiotic, which has reduced its effectiveness for treating some types of infection. Oxytetracycline works by interfering with the ability of bacteria to produce proteins that are essential to them. In humans, oxytetracycline is used to treat infections of the respiratory and urinary tracts, skin, ear, eye and gonorrhoea, although the use of tetracyclines for such purposes has declined in recent years due to large increases in bacterial resistance to this class of drugs. In animals, oxytetracycline is used to control the outbreak of American Foulbrood and European Foulbrood in honeybees. It can also be used to correct breathing disorders in livestock. In addition, it is sometimes administered in feed to prevent diseases and infections in cattle and poultry.
In the Netherlands, oxytetracycline is registered as a human pharmaceutical in three products, eardrops, and ear- and eye ointments [4]. No use data for oxytetracycline could be found in the GIP-databank [5]. For humans, doxycycline is by far the most prescribed drug, followed by minocycline and tetracycline. However, for veterinary use 55 products are registered [4]. The compound is not included in the Pollutant Release and Transfer Register [6].

16.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human and veterinary pharmaceutical in NL

16.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
DK	10	AA-EQS, AF 10 on EC_{10} for cyanobacteria	[76]
DK	21	MAC-EQS, AF 10 on EC_{50} for cyanobacteria	[76]
F	1.83	PNEC, AF 100 on NOEC for algae	[70]
N	0.2	PNEC, not further specified	[27]
UK	45	PNEC, AF 100 on EC50 for algae	[63]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

16.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	Carc2 Repr2	self classification	[77]
	H301, 315, 319, 335, 361, 362, 410	notified classification	[8]
log K_{ow}	-0.90	experimental EpiSuite	[1]
BCF	1 L/kg	estimated worst case	[17]
Human toxicological threshold limit (TL_{hh})	0-0.03 mg/kg bw		[78]
	0-0.003 mg/kg bw	see remark below	[79]

In the EMEA evaluation [79], it is stated that the ADI as proposed by JECFA is used, however, a 10-times lower value is mentioned than in the JECFA-documents. The JECFA-value is used here.

16.7 Environmental concentrations

16.7.1 Netherlands

In 2004, oxytetracycline was not detected in surface water and sediment in the vicinity of intensive husbandry farms [80]. It should be noted that the analysis of oxytetracycline is difficult, and recovery is generally low, especially in small waters.

Schrap et al. [33] report incidental high peaks of oxytetracycline in STP-influents. Concentrations of 1.3 and 4.4 µg/L were measured at two STPs, the sources of the emissions were unclear but probably related to cattle breeding or fish farming.

Schilt and Van de Lagemaat [81] did not observe any tetracyclines in groundwater.

In 2009, the Stichting Toegepast Waterbeheer (STOWA) performed a study into the emissions of pharmaceuticals from hospitals. Case studies were performed at Stadskanaal, Leiden and Nieuwegein [82-84]. Tetracyclines, including doxycycline, mecocycline and oxytetracycline, were not detected above the detection limit in hospital discharge water (detection limit 0.4-1 μg/L) nor in influents and effluents of the local STP (detection limits 0.2-0.4 μg/L).

In 2010, extracts of residues in passive samplers (POCIS and silicone rubbers) were tested for antibiotic activity using a plate counting method. In none of the samples tetracycline activity was detected [34].

16.7.2 *Other countries*

A selection of data from other countries is presented. Concentrations in surface water of 4.5 μg/L are reported in [63], measured on a 'hotspot', i.e. at a site where intensive pig rearing occurs. Concentrations of around 0.1 μg/L are reported for in surface waters from an agricultural area in the USA [85]. Oxytetracycline was not detected in surface water from a wetland in Spain [86].

It should be noted that oxytetracycline has a relatively high sorption coefficient and low DT_{50} in soil (K_{oc} 28,000-93,000 L/kg; DT_{50} 18 days, data from Boxall et al., 2007). This could be the reason that emissions to soil via application of manure do no result in detectable concentrations in surface water.

In a recent report of the German Umweltbundesamt, measured concentrations > 1 μg/L are reported for surface water [87].

16.8 Removal upon water treatment

Oxytetracycline is not put forward as a drinking water relevant substance by the RIWA.

16.9 Environmental risk limits based on direct ecotoxicity

The AA-EQS of 10 μg/L used in Denmark is based on an EC_{10} for cyanobacteria of 100 μg/L with an assessment factor of 10. The French PNEC is based on a chronic endpoint for green algae (NOEC 183 μg/L), but with an assessment factor of 100. Boxall et al. [63] derived a PNEC of 45 μg/L using an EC_{50} for algae that is also reported by the Danish EPA (4.5 mg/L) with an assessment factor of 100. Jones et al. [88] report PNECs of 0.23 μg/L for cyanobacteria and 4.5 μg/L for algae on the basis of the same endpoints that were used in the Danish assessment, most likely using an assessment factor of 1000 on the respective EC_{50}-values (although that would lead to a value of 0.21 instead of 0.23 for cyanobacteria).
According to the guidance, an assessment factor of 10 can only be applied when chronic data for fish, algae and *Daphnia* are present. Chronic data on fish are absent, but from the data and mode of action it appears that algae and cyanobacteria are by far the most sensitive taxa, and an assessment factor of 10 on the lowest value for algae/cyanobacteria is considered justified. In that respect, the PNEC as derived by the Danish EPA would be correct.
In some recent studies, however, much lower endpoints are observed than used in the Danish assessment. In the MistraPharma database [89] a NOEC of 3.1 μg/L is reported for cyanobacteria, originating from a 144-hours test with *Anabaena cylindrica* [90]. NOECs for other cyanobacteria reported by these authors are also lower than used in the Danish assessment (25 μg/L for *Anabaena flos-aquae*, 31 μg/L for *Microcystis aeruginosa*). In addition, EC_{10}-values of 48-62 μg/L are reported in the US EPA Ecotox database [39] from a microcosm study [91]. Based on the lowest NOEC of 3.1 μg/L, a chronic ERL for direct ecotoxicity of 0.31 μg/L is used in the present assessment.

16.10 Environmental risk limits based on secondary poisoning

Not relevant.

16.11 Environmental risk limits based on human toxicology

16.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.03 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.03 x 0.1 x 70) / 2 = 0.105 mg/L = 105 µg/L.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

16.11.2 Surface water for fish consumption

Probably relevant because of H361, 362 (notified classification).

Input: TL_{hh} = 0.03 mg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 1 L/kg (estimated worst case value).
ERL (food) = (0.03 x 0.1 x 70) / 0.115 = 0.061 mg/kg fish.
ERL (water) = 0.061 / 1 = 0.061 mg/L = 61 µg/L.

16.12 Summary and discussion

Several (proposals for) PNECs or water quality standards are available, the lowest value is the chronic AA-EQS of 10 µg/L according to the Danish EPA. However, endpoints for cyanobacteria and aquatic macrophytes from recent literature are lower than the most critical endpoint used in the Danish dataset. Based on these data, a PNEC of 0.31 µg/L is derived. Based on the TL_{hh} for oxytetracycline as established by JECFA [78], a drinking water limit of 105 µg/L is derived, which is much higher than the DMR-target value of 0.1 µg/L. In view of the widespread use in livestock breeding, one would expect that emissions occur and that the compound would be found in surface water. The few monitoring results so far do not indicate, however, that the compound is present in surface water in the Netherlands. This might be due to the fate and behaviour of the compound (sorption, degradation). It should be noted, however, that analysis of oxytetracycline in water is difficult and recoveries are generally low. Furthermore, emissions to surface water, if any, are expected to occur at relatively small water bodies which are not included in the regular monitoring programs of the RIWA and the Waterdienst.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	0.31	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	105	µg/L
ERL human fish consumption	61	µg/L
Environmental concentration	?	µg/L
Risk ratio		ERL DMR
		ERL DW
		ERL ECO

n.r. = not relevant

16.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and not relevant for drinking water, because the compound is not detected;
- potentially relevant for ecology due to short-term peaks, but the chance of detecting those peaks during normal monitoring is limited.

Recommendation

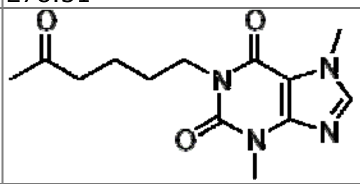
- investigate options for alternative monitoring approaches and search for additional data.

17 Pentoxifylline

17.1 Introduction

Pentoxifylline is put forward by the RIWA as a drinking water relevant compound because it is toxicologically relevant and frequently present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may give rise to public concern, and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

17.2 Chemical identity

Name	Pentoxifylline
Chemical name	1-(5-oxohexyl)-3, 7-dimethylxanthine
CAS number	6493-05-6
EC number	229-374-5
Molecular formula	$C_{13}H_{18}N_4O_3$
Molar mass	278.31
Structural formula	
SMILES code	CC(=O)CCCCN1C(=O)N(C)c2ncn(C)c2C1=O

17.3 Information on uses and emissions

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disorders. Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine TNFα, and this property is under investigation in several diseases [92]. One product is registered in the Netherlands, tradename Trental [4], 12 products are registered in Germany [92]. Information from the GIP-databank [5] reveals that the estimated number of users has declined from 3364 in 2006 to 2118 in 2010. The total use amounted to 516 kg in 2007 (Monique van der Aa, pers. comm.), more recent figures are not available. The therapeutic value is indicated as marginal [93]. The compound is not included in the Pollutant Release and Transfer Register [6].

17.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human pharmaceutical in NL

17.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

17.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 312, 332	notified classification	[8]
log K_{ow}	0.29	experimental EpiSuite	[1]
BCF	<100	estimated using log K_{OW}	[17]
Human toxicological threshold limit (TL_{hh})	not available		

17.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2006	<	<	<		4 (Brakel)	[12]
	<	0.13	0.0442	0.127	12 (Lobith)	
	<	0.21	0.0483	0.177	12 (Nieuwegein)	
	<	0.13	0.0404	0.118	13 (Nieuwersluis)	
	<	0.03	0.0119	0.03	13 (Andijk)	
2007	<	<	<		4 (Brakel)	[12]
	<	0.058	<	0.0388	13 (Lobith)	
	<	0.02	<	0.02	13 (Nieuwegein)	
	<	0.01	<	<	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2008	<	<	<		3 (Heel)	[12]
	<	<	<		4 (Brakel)	
	<	0.18	0.0325	0.168	13 (Lobith)	
	<	0.05	0.0127	0.046	11 (Nieuwegein)	
	<	0.05	0.0112	0.044	12 (Nieuwersluis)	
	<	0.02	<	0.0155	12 (Andijk)	
2009	<	<	<		1 (Heel)	[12]
	<	<	<		4 (Brakel)	
	<	0.04	0.0102	0.034	13 (Lobith)	
	<	0.03	0.0108	0.026	13 (Nieuwegein)	
	<	0.04	0.0104	0.032	13 (Nieuwersluis)	
	<	0.02	<	0.014	13 (Andijk)	
2010	<	<	<	<	12 (Brakel)	[12]
	<	<	<		4 (Keizersveer)	
	<	0.017	<	0.0155	12 (Lobith)	
	<	0.02	<		7 (Nieuwegein)	
	<	0.02	<		7 (Nieuwersluis)	
	<	<	<		7 (Andijk)	
	<	<	<		4 (Stellendam)	

In 2010, it was detected in January and April at Lobith, and in May at Nieuwegein and Nieuwersluis [12,50], the highest concentration was 0.02 µg/L.

The monitoring data suggest that emissions of pentoxifylline decline since 2006, which is consistent with the decline in the number of users. However, analysing the data series as from 2002, the RIWA observed a significant increase at Andijk in 2009 as compared to 2005-2008. At Lobith, the data from 2010 indicate a significant decreasing trend as compared to 2004-2009.

In 2010, pentoxifylline was not detected in STP-influents and effluents by Water board Rijnland.

17.8 Removal upon water treatment

Based on an estimated log Kow of 0.56, VP of 1.22E-10 and BIOWIN3 value of 2.5617 (months to recalcitrant), pentoxifylline is considered difficult to remove by the current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

17.9 Environmental risk limits based on direct ecotoxicity

No regulatory standard or reliable proposal is available. No ecotoxicological data could be found in databases or on the internet. Thus, no ERL can be derived for direct ecotoxicity.

17.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

17.11 Environmental risk limits based on human toxicology

17.11.1 Surface water for drinking water abstraction

A human toxicological threshold limit (TL_{hh}) is not available. According to the CBG-website [4], the recommended dose is 400 mg once or twice a day. For other pharmaceuticals, the lowest therapeutic dose was used with an assessment factor of 100 to establish a provisional TL_{hh} [11]. For pentoxifylline this would lead to a value of 4 mg per person per day.

Input: TL_{hh} = 4 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (4 x 0.1) / 2 = 0.2 mg/L = 200 µg/L.
If pentoxifylline is put forward for further actions, this information should be checked by experts.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

17.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

17.12 Summary and discussion

No information on ecotoxicity is available, recent monitoring data indicate that concentrations are well below the DMR-target value of 0.1 µg/L. Furthermore, there is a continuing trend toward declining concentrations as from 2006.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	?	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	200	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.02	µg/L
Risk ratio	0.2	ERL DMR
	0.0001	ERL DW
	?	ECO

n.r. = not relevant

17.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90th percentile concentrations in 2007, 2009 and 2010 are lower than the DMR-target value. The therapeutic relevance is questioned and a further decline in use is expected, which is consistent with the observed decline in locations and frequency of detection in 2010 as compared to previous years.

- Relevance for ecology is unknown, because ecotoxicity data are not available.

Recommendation

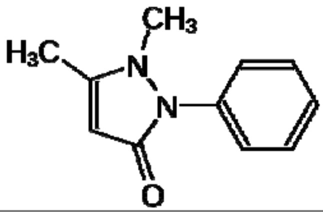
- continue monitoring to determine whether or not the decreasing trends continue.

18 Phenazone

18.1 Introduction

Phenazone is proposed by the RIWA as a drinking water relevant compound, because it is present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may rise public concern and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

18.2 Chemical identity

Name	Phenazone, fenazone
Chemical name	1,2-dihydro- 1,5-dimethyl- 2-phenyl- 3H-pyrazol- 3-one
CAS number	60-80-0
EC number	200-486-6
Molecular formula	C11H12N2O
Molar mass	188.22
Structural formula	
SMILES code	CN1N(C2=CC=CC=C2)C(=O)C=C1C

18.3 Information on uses and emissions

Phenazone is an analgesic and antipyretic that has been given by mouth and as ear drops. In the Netherlands, phenazone is not registered as a human pharmaceutical [4]. The GIP-databank does provide information until 2008. In Germany it is registered against migraine, while in several countries (Germany, Belgium, Switserland, France) it is used in eardrops. It is available via Dutch websites. The compound is not included in the Pollutant Release and Transfer Register [6].
It might be possible that phenazone is a degradation product of propyphenazone. That compound is used in several products that can be purchased over-the-counter [92].

18.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No (log Kow 0.4)
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as pharmaceutical in NL D: Classified as water hazardous class 1 [14]

18.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

18.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	Muta2 AcuteTox4 Mut3;R68;R22	advised self classification	[77]
	H302, 315, 317, 319, 335	notified classification	[8]
log K_{ow}	0.4	estimated	[10]
	0.4	experimental	[1]
BCF	0.44	estimated with log K_{ow} 0.4	[17]
Human toxicological hreshold limit (TL_{hh})	2.5 mg/person	provisional ADI	[11]

18.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2005		0.11				26 datapoints; data from RIWA	[10]
2005	0.012	0.132				5 datapoints, autumn 2005	[11]
2006	0.011	0.033				2 datapoints, spring 2006	
2006	<	<	*	<	*	4 (Brakel)	[12]
	<	0.02	<	<	0.016	13 (Nieuwegein)	
	<	0.03	0.01	0.0129	0.03	12 (Nieuwersluis)	
	<	0.02	<	<	0.016	13 (Andijk)	
2007	<	<	*	<	*	4 (Brakel)	[12]
	<	0.02	<	<	0.016	13 (Nieuwegein)	
	<	0.03	0.01	0.0129	0.03	12 (Nieuwersluis)	
	<	0.02	<	<	0.016	13 (Andijk)	
2008	<	<	*	<	*	7 (Liège)	[12]
	<	<	*	<	*	4 (Brakel)	
	<	<	*	<	*	9 (Keizersveer)	
	<	0.02	<	<	0.02	11 (Nieuwegein)	
	<	0.02	0.015	0.0145	0.02	10 (Nieuwersluis)	
	<	0.01	<	<	0.01	12 (Andijk)	
2009	*	*	*	*	*	1 (Heel)	[12]
	<	<	*	<	*	4 (Brakel)	
	<	0.01	<	<	<	15 (Keizersveer)	
	<	0.03	<	0.0125	0.027	12 (Nieuwegein)	
	0.01	0.02	0.01	0.013	0.02	10 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
2010	<	<	*	<	*	4 (Namêche)	[12]
	<	<	*	<	*	4 (Liège)	
	<	<	<	<	<	13 (Brakel)	
	<	<	<	<	<	13 (Keizersveer)	
	<	0.23	0.01	0.0291	0.154	13 (Nieuwegein)	
	<	0.03	0.01	0.0148	0.0284	13 (Nieuwersluis)	
	<	0.027	<	<	0.0242	13 (Andijk)	
	<	0.03	<	<	0.027	12 (Stellendam)	

The overall average of the 90th percentile concentrations in Dutch sampling points of RIWA over 2010 is 0.06 µg/L.

Concentrations in raw water ranged from 0.011 to 0.152 µg/L in autumn 2005, and from 0.011 to 0.108 µg/L in spring 2006 (Versteegh et al. (2007)).

In 2008 and 2009, Water board Roer and Overmaas did not detect phenazone above the reporting limit (0.025 µg/L) in the River Roer.

In a research project with passive samplers, phenazone was detected on several locations. Based on the residues in POCIS samplers, estimated concentrations in water ranged from 0.8 to 2.4 ng/L [34]. This is higher than the concentrations reported by RIWA, which may be due to methodological differences.

18.8 Removal upon water treatment

Based on a log K_{ow} of 0.59, VP of 0.000279 and BIOWIN3 value of 2.8052 (weeks to months), phenazone is considered difficult to remove by simple surface water treatment, however it might be removed (40-100%) by rapid filtration ('snelfiltratie'). Implementation of this technique implies that reduction of the level of purification treatment will not be possible.

18.9 Environmental risk limits based on direct ecotoxicity

Regulatory standards or reliable proposals are not available. Phenazone is not included in the German ETOX database [44], US EPA Ecotox [39], and a quick scan for relevant papers in the open literature did not result in any useful references. The following data are available from IUCLID [94]:
96-hours LC_{50} *Danio rerio*: > 500 mg/L (OECD 203, GLP);
48-hours EC_{50} *Bacillus subtilis*: 16.9 g/L (no details available).
With an assessment factor of 1000 on the LC_{50} for fish, a tentative PNEC of > 500 µg/L is derived.

18.10 Environmental risk limits based on secondary poisoning

Not relevant.

18.11 Environmental risk limits based on human toxicology

18.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 2.5 mg person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since the TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (2.5 x 0.1) / 2 = 0.125 mg/L = 125 µg/L.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

18.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

18.12 Summary and discussion

The information on direct ecotoxicity is limited, based on non-evaluated data direct ecotoxicity does not seem to be relevant. The monitoring dataset is quite extensive. The monitoring data of the RIWA indicate that at some locations the compound is not often detected above the limit of quantification (0.01 µg/L), while the LOQ is sufficiently low as compared to the DMR-target value of 0.1 µg/L. At other locations such as Nieuwegein, the compound is detected more often, but the 90th percentile in 2010 seems to be determined by one high value, measured in September. Based on the average 90th percentile of 0.06 µg/L and the drinking water limit of 125 µg/L, the risk ratio is 0.005. Using the DMR-target value of 0.1 µg/L, the risk ratio is 0.2.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	> 500	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	125	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.06	µg/L
Risk ratio	0.6	ERL DMR
	0.005	ERL DW
	<0.01	ERL ECO

n.r. = not relevant

18.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90th percentile concentrations are lower than the DMR-target value except for one location in 2010; found at 4 locations, data suggest an incidental peak in 2010 at one location; human-toxicological risk limit >> DMR-target value;
- not relevant for ecology because the risk ratio is <0.01.

Recommendation

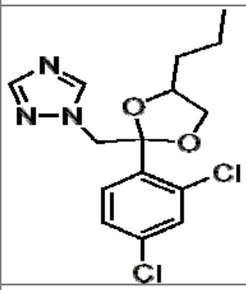
- continue monitoring.

19 Propiconazole

19.1 Introduction

Propiconazole is proposed by the Waterdienst as a potential relevant compound. It is detected in surface waters and is selected for further screening based on its ecotoxicity (Grontmij | Aquasense, 2010).

19.2 Chemical identity

Name	Propiconazole
Chemical name	(±)-1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl] methyl]-1H-1,2,4-triazole
CAS number	60207-90-1
EC number	262-104-4
Molecular formula	C15H17Cl2N3O2
Molar mass	342.2
Structural formula	
SMILES code	Clc1ccc(c(Cl)c1)C2(OCC(O2)CCC)Cn3ncnc3

19.3 Information on uses and emissions

Propiconazole is used as a biocide in wood preservation and as a fungicide in agriculture. In agriculture, the area on which it is used has decreased from 21,242 ha in 2004 to 5253 ha in 2008 (4.5-1.0% of the area treated with fungicides). The total amount used in agriculture declined from 2201 kg in 2004 to 782 kg in 2008 [95]. Use figures for application as biocide are not available. Estimated emissions to surface water were 1 kg/y in 2005, and 0 kg/y in 2007 and 2008 [6].

19.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Included in Annex I
Biocides (98/8/EC)	Included in Annex I for Pt 8; to be phased out for Pt 1, 2, 4, 13
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as agricultural fungicide and biocide in NL

19.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	0.1	legal MKN value for pesticides/biocides in surface water for abstraction of drinking water	[35]
NL	10[1]	indicative MPC_{water}	[48]
EU	1.6	PNEC from biocides risk assessment	[96]
	0.1	target value for biocides in surface water for abstraction of drinking water	[7]

1: most likely not approved by Stuurgroep Stoffen, since not included on www.rivm.nl/rvs

19.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 317, 400, 410	harmonised classification	[8]
log K_{ow}	3.72		[96,97]
BCF	116 L/kg 180 L/kg	experimental; whole fish experimental; whole fish	[96,97]
Human toxicological threshold limit (TL_{hh})	0.04 mg/kg bw.d	ADI	[97]

19.7 Environmental concentrations

In 2005, propiconazole was not detected during screening monitoring in concentrations above the limit of quantification (0.05 µg/L) [98].

From 2006 to 2010, propiconazole was not detected at RIWA sampling points at concentrations above the reporting limit, except for 2008 when a maximum and 90^{th} percentile of 0.07 and 0.052 µg/L are reported for Heel [12,50].

In 2009, propiconazole was detected three times during screening monitoring by the Waterdienst [30]. In 2010, it was not detected at sampling points of the Waterdienst, except for three times at Sas van Gent (maximum 0.1 µg/L) and once at Nederweert (0.07 µg/L) [22].

Monitoring data for surface water were provided by the Water board Hollandse Delta (Province of South-Holland). Between 1995 and 2001, propiconazole was never detected above the reporting limit (0.05 µg/L).

Propiconazole was included in the screening monitoring by the Water board Brabantse Delta in 2011. Concentrations were below the reporting limit of 0.06 µg/L, except for three locations with concentrations of 0.07 and 0.08 µg/L.

Monitoring data of the Water board Rijnland over 2007 and 2008 are summarised in the table below. The 90^{th} percentile concentration of 14.8 µg/L measured in 2008 is higher than the indicative MPC of 10 µg/L, the other data are lower. Information from the Water board reveals that the high concentration in 2008 was measured in a small ditch, which is not representative for the area in general. As from 2008, propiconazole was not included in the monitoring program anymore.

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark
2007	0.04	0.57			0.36	polderwater
2007	0.04	0.68			0.23	polderwater
2007	0.61	12			6.58	polderwater
2008	0.03	0.12			0.11	polderwater
2008	0.04	0.11			0.09	polderwater
2008	0.32	77			14.80	polderwater

The Water board Roer and Overmaas (Province of Limburg) provided monitoring data for 2009-2010. In 2010, 15 locations were analysed for propiconazole on more than one date. Concentrations were below the reporting limit in the majority of cases, in a few occasions propiconazole was detected at concentrations between 0.02 and 0.09 µg/L. In 2010, propiconazole was never detected above the reporting limit (0.02 µg/L).

Monitoring data from 11 water boards over 2000-2009 show that propiconazole was not detected in concentrations higher than the water quality standard, which is most likely the indicative MPC of 10 µg/L (Gezamenlijk meetnet bestrijdingsmiddelen 2000-2009).

In 2011, propiconazole was not detected by six water boards which have their samples analysed by Water board Groot Salland.

According to the Bestrijdingsmiddelenatlas, the indicative MPC of 10 µg/L was never exceeded in 2009. The target value (0.01 times the MPC) is exceeded on four locations, one of which is a WFD-monitoring location. An average concentration of about 15 ng/L is reported for 2009. This is most likely based on calculations in which for non-detects half of the detection limit is used as result. Concentrations show a constant decline as from 1997.

Concentrations in STP-effluents are 0.09 µg/L (average), 0.19 µg/L (90^{th} percentile), maximum is 0.22 µg/L (n=6; WD data).

19.8 Removal upon water treatment

Propiconazole is not put forward as a specific drinking water relevant substance by RIWA. Since the compound is a pesticide/biocide, it is included in the BKMW.

19.9 Environmental risk limits based on direct ecotoxicity

The data underlying the indicative MPC cannot be retrieved. Based on the EU-biocides dossier, the PNEC is 1.6 µg/L. Since this value is lower than the indicative MPC and based on a more recent evaluation, it is used for the present assessment.

19.10 Environmental risk limits based on secondary poisoning

The lowest relevant NOEC for mammals is 20 mg/kg fd from a 17-weeks study in mice [97]. With an assessment factor of 30, the PNECoral is 0.67 mg/kg fd. Using the BCF of 180 L/kg, the resulting PNEC for water is 0.0037 mg/L = 3.7 µg/L.

19.11 Environmental risk limits based on human toxicology

19.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.04 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.04 x 0.1 x 70) / 2 = 0.14 mg/L = 140 µg/L.

The proposed target value for pesticides and biocides according to the DMR-memorandum is 0.1 µg/L, in line with EU Directive 98/83/EC. This limit is also implemented in the BKMW.

19.11.2 Surface water for fish consumption

Input: TL_{hh} = 0.04 mg/kg bw.d, 115 g fish per day, body weight 70 kg; 10% of TL_{hh} allowed via fish consumption, BCF = 180 L/kg.
ERL (food) = (0.04 x 0.1 x 70) / 0.115 = 2.4 mg/kg fish.
ERL (water) = 2.4 / 180 = 0.014 mg/L = 14 µg/L.

19.12 Summary and discussion

According to the Bestrijdingsmiddelenatlas, the indicative MPC of 10 µg/L was not exceeded in 2009. The PNEC of 1.6 µg/L is about a factor of six lower than the indicative MPC of 10 µg/L, but this will not change the conclusion since at 218 out of 222 sampling points the concentrations were below the target value (1/100 of the MPC, 0.1 µg/L). At four sampling points, the concentration was between 0.1 and 10 µg/L, but according to the raw data concentrations were always below 1 µg/L. Furthermore, a strong decline is noted in the agricultural use. The 90^{th} percentile of concentrations in STP-effluents is 0.19 µg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.02 µg/L which is in accordance with measured data.
Based on the reported average concentration in the Bestrijdingsmiddelenatlas of 15 ng/L in 2009 (0.015 µg/L), the risk ratio based on the PNEC is 0.009. Based on the quality standard for drinking water abstraction of 0.1 µg/L, the risk ratio is 0.15.

MKN BKMW	0.1	µg/L
ERL direct ecotoxicity	1.6	µg/L
ERL secondary poisoning	3.7	µg/L
ERL drinking water	140	µg/L
ERL human fish consumption	14	µg/L
Environmental concentration	0.015	µg/L
Risk ratio	0.15	MKN BKMW
	0.0001	ERL DW
	0.009	ERL ECO

19.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the quality standard for pesticides of the BKMW;
- not relevant for ecology because the risk ratio is <0.01.

Recommendation

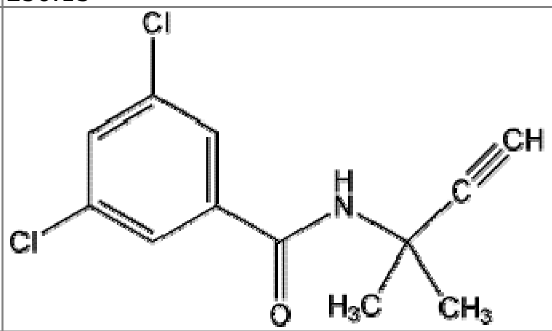
- no further actions, consider not to include in watch list.

20 Propyzamide

20.1 Introduction

Propyzamide is proposed by the Waterdienst as a potential relevant compound. It is detected in surface waters and is selected for further screening based on its ecotoxicity [30].

20.2 Chemical identity

Name	Propyzamide
Chemical name	3,5-dichloro-N-(1,1-dimethylprop-2-ynyl)benzamide
CAS number	23950-58-5
EC number	245-951-4
Molecular formula	C12H11Cl2NO
Molar mass	256.13
Structural formula	
SMILES code	Clc1cc(C(=O)NC(C#C)(C)C)cc(Cl)c1

20.3 Information on uses and emissions

Propyzamide is used as a herbicide. The area on which it is used has increased from 7962 ha in 2004 to 8525 ha in 2008 (1.0-1.1% of the area treated with herbicides). However, the total amount used declined from 7869 kg in 2004 to 6077 kg in 2008 [95]. Estimated emissions to surface water were 1 kg/y in 2005, 2007 and 2008 [6].

20.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414/EEC)	Included in Annex I
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as herbicide in NL.

20.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	0.1	legal MKN for pesticides in surface water for abstraction of drinking water	[35]
	11[1]	indicative MPC_{water}	[48]
	0.1	target value for pesticides in surface water for abstraction of drinking water	[7]

1: most likely not approved by Stuurgroep Stoffen, since not included on www.rivm.nl/rvs

20.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H351, 400, 410	harmonised classification	[8]
log K_{ow}	3.0		[99]
BCF	49 L/kg	experimental; whole fish	[99]
Human toxicological threshold limit (TL_{hh})	0.02 mg/kg bw.d	ADI	[99]

20.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2006	<	<	<	<	<	13(Brakel)	[10]
2006	<	<	<	<	<	13 (Keizersveer)	[12]
2007	<	<	<	<	<	13 (Brakel)	[12]
	<	<	<	<	<	13 (Keizersveer)	
2008	<	<		<		1 (Liège)	[12]
	<	<	<	<	<	13 (Brakel)	
	<	<	<	<	<	13 (Keizersveer)	
	<	<	<	<	<	13 (Nieuwegein)	
2009	<	<		<		3 (Liège)	[12]
	<	<	<	<	<	13 (Brakel)	
	<	<	<	<	<	13 (Keizersveer)	
	<	<	<	<	<	13 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
2009	<	<			<	polderoutlet	data from water board Rijnland
	<	0.04			0.02	polderoutlet	
	<	<			<	polderoutlet	
	<	0.03			0.01	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderwater	
	<	0.26			0.124	polderwater	
	<	0.04			0.03	polderwater	
	<	0.1			0.067	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	0.13			0.094	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2010	<	<			<	polderoutlet	data from water board Rijnland
	<	0.1			0.01	polderoutlet	
	<	<			<	polderoutlet	
	<	0.04			0.01	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderoutlet	
	<	<			<	polderwater	
	<	0.05			0.03	polderwater	
	<	0.12			0.03	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	0.03			0.029	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	0.02			0.019	polderwater	
	<	0.14			0.01	polderwater	
	<	0.05			0.028	polderwater	
	<	0.03			0.01	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	0.12			0.019	polderwater	
	<	0.05			0.028	polderwater	
	<	<			<	polderwater	
	<	0.46			0.037	polderwater	
	<	0.12			0.076	polderwater	
	<	0.08			0.04	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
	<	<			<	polderwater	
2010	<	<		<		4 (Namêche)	[12]
	<	0.016		<		4 (Liège)	
	<	<	<	<	<	13 (Brakel)	
	<	<	<	<	<	13 (Keizersveer)	
	<	0.02	<	<	<	13 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<	<	<	<	13 (Andijk)	
2010	0.007	0.037				Lobith, 13 data points, 11 <RL	data from Waterdienst

RL = reporting limit; lowest concentration that can be quantified accurately

In 2005, propyzamide was detected in concentrations above the reporting limit of 0.01 µg/L at three locations. The highest concentration was 0.05 µg/L at Schaar van Ouden Doel [98].

Monitoring data from 11 water boards over 2000-2009 show that propyzamide was not detected in concentrations higher than the water quality standard, which is most likely the indicative MPC of 11 µg/L (Gezamenlijk meetnet bestrijdingsmiddelen 2000-2009). One of the participating water boards, Wetterskip Fryslân, reports concentrations between 0.01 and 0.22 µg/L over 2009 and 2010.

In 2009, propyzamide was detected seven times during screening monitoring by the Waterdienst [30].

In 2009, propyzamide was not detected above the reporting limit of 0.025 µg/L during monitoring by the Water board Roer and Overmaas (Province of Limburg).

Monitoring data for groundwater and surface water were provided by the Water board Hollandse Delta (Province of South-Holland). Propyzamide was not analysed at the WFD-monitoring locations.
Data from the regular pesticide monitoring program were also provided, results for 2009-2011 are summarised here. About 90 locations were sampled three or four times, the majority of samples showed concentrations below the reporting limit. In 2009, propyzamide was detected more than once at a number of different locations, but concentrations were generally lower than 0.1 µg/L. At four locations, higher peaks were detected (0.17-0.64 µg/L). In 2010, the maximum concentration was 0.1 µg/L, while in 2011 the highest measured concentration was 0.04 µg/L.

In 2011, propyzamide was not detected above the reporting limit of 0.01 µg/L during screening monitoring by the Water board Brabantse Delta (Province of North-Brabant).

Monitoring data for 2011 were provided for six water boards which have their samples analysed by the Water board Groot Salland. Propyzamide was detected eight times on four locations, concentrations ranged from 0.01 to 0.13 µg/L, the average was 0.05 µg/L.

In the Bestrijdingsmiddelenatlas, average concentrations of 7-13 ng/L are reported for 2009. This is most likely based on calculations in which for non-detects half of the reporting limit is used as result. The indicative MPC of 11 µg/L was never exceeded in 2009, the target value (0.01 times the MPC) is exceeded on 11 locations, two of which are WFD-monitoring locations.

Concentrations in STP-effluents are 0.02 µg/L (average, maximum and 90th percentile) (n=2; WD data). The Water board Rijnland reports non-detectable concentrations in STP-effluent, and a maximum concentration of 0.1 µg/L in STP-influent.

20.8 Removal upon water treatment

Propyzamide is not put forward as a specific drinking water relevant substance by the RIWA. Since the compound is a pesticide, it is included in the BKMW.

20.9 Environmental risk limits based on direct ecotoxicity

The indicative MPC of 11 µg/L is based on the NOEC for *Lemna sp.* of 0.56 mg/L from the EU-dossier, with an assessment factor of 50. This factor is probably used because a NOEC for algae is not reported in the EU list of endpoints. From the underlying dossier it appears that the NOEC for *Lemna sp.* might indeed not be protective for algae. Based on the study summaries, the NOEC for *Anabaena flos-aquae* is probably 0.19 mg/L. The indicative MPC of 11 µg/L is selected.

20.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF < 100 L/kg).

20.11 Environmental risk limits based on human toxicology

20.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.02 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.02 x 0.1 x 70) / 2 = 0.07 mg/L = 70 µg/L.

The proposed target value for pesticides according to the DMR-memorandum is 0.1 µg/L, in line with EU Directive 98/83/EC. This limit is also implemented in the BKMW.

20.11.2 Surface water for fish consumption

Input: TL_{hh} = 0.02 mg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 49 L/kg.
ERL (food) = (0.02 x 0.1 x 70) / 0.115 = 1.22 mg/kg fish.
ERL (water) = 1.22 / 49 = 0.025 mg/L = 25 µg/L.

20.12 Summary and discussion

The indicative MPC is based on the data in the EU-dossier and is considered adequate. According to the Bestrijdingsmiddelenatlas, the indicative MPC of 11 µg/L was not exceeded in 2009. Monitoring data from Water board Hollandse Delta indicate that in that area concentrations in 2010 and 2011 have declined as compared to 2009. However, incidental peaks may occur, which is also demonstrated by the analysis results from the Water board Groot Salland. Concentrations in STP-effluents are 0.02 µg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.002 µg/L (2 ng/L) which is in accordance with most measured data.
According to the Bestrijdingsmiddelenatlas, the target value of (0.01 times MPC) is exceeded on 11 locations, two of which are WFD-monitoring locations. This means that on these locations the risk ratio based on the indicative MPC is > 0.01. In view of the data provided by water boards, this is most likely due to incidental peaks. Using the overall average concentration, the risk ratio based on indicative MPC is at most 0.001 and it is most likely that this also holds for the 90^{th} percentile on individual locations. Based on the quality standard for drinking water abstraction of 0.1 µg/L, the risk ratio is 0.07–0.13.

MKN BKMW	0.1	µg/L
ERL direct ecotoxicity	11	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	70	µg/L
ERL human fish consumption	25	µg/L
Environmental concentration	0.007-0.013	µg/L
Risk ratio	0.07-0.13	MKN BKMW
	0.0001-0.002	ERL DW
	0.0006-0.001	ERL ECO

n.r. = not relevant

20.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the quality standard for pesticides of the BKMW;
- not relevant for ecology because the risk ratio is <0.01.

Recommendation

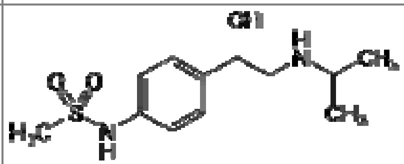
- no further actions, consider not to include in watch list.

21 Sotalol

21.1 Introduction

Sotalol is put forward by the RIWA as a drinking water relevant compound because it is toxicologically relevant and frequently present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may give rise to public concern, and the risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

21.2 Chemical identity

Name	Sotalol
Chemical name	(RS)-N-{4-[1-hydroxy-2-(propan-2-ylamino) ethyl]phenyl}methanesulfonamide
CAS number	3930-20-9
EC number	213-496-0
Molecular formula	$C_{12}H_{20}N_2O_3S$
Molar mass	272.37
Structural formula	
SMILES code	CC(C)NCC(O)c1ccc(NS(C)(=O)=O)cc1

21.3 Information on uses and emissions

Sotalol (as sotalol hydrochloride) is registered as a human pharmaceutical in the Netherlands. Sotalol is a non-selective β-adrenergic receptor blocker that is used against rhythm disturbances of the heart and to treat hypertension. In the Netherlands, 18 products are registered [4]. The estimated number of users was 116,000 in 2006 and has slightly decreased to 110,000 in 2010 [5]. In 2007, the total amount used was 3992 kg, while the use is expected to increase to 5146 kg in 2020 [23]. The compound is not included in the Pollutant Release and Transfer Register [6].

21.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as human pharmaceutical in NL

21.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-		
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

21.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	-	not included in ESIS or C&L inventory	[8,9]
log K_{ow}	0.39	estimated EpiWin	[1]
	0.24	experimental EpiWin	[1]
BCF	3.162 L/kg	estimated with log K_{ow}	[1]
Human toxicological threshold limit (TL_{hh})	not available		

21.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90^{th} percentile [µg/L]	Remark	Reference
2006	<	0.07	<		4 (Brakel)	[12]
	<	0.14	<	0.124	13 (Nieuwegein)	
	<	0.2	0.0879	0.188	12 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2007	<	<	<		4 (Brakel)	[12]
	0.012	0.046	0.0226	0.0433	12 (Lobith)	
	<	0.07	<	0.052	13 (Nieuwegein)	
	<	0.11	0.0731	0.106	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2008	0.059	0.094	0.0793		4 (Heel)	[12]
	<	<	<		4 (Brakel)	
	0.043	0.15	0.102		9 (Keizersveer)	
	0.013	0.033	0.0233	0.0322	13 (Lobith)	
	<	0.07	<	0.052	13 (Nieuwegein)	
	<	0.12	0.0854	0.117	12 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
2009	<	<	<		3 (Brakel)	[12]
	0.017	0.057	0.0347	0.0554	13 (Lobith)	
	<	0.07	<	0.067	12 (Nieuwegein)	
	<	0.17	0.0959	0.162	11 (Nieuwersluis)	
	<	<	<	<	12 (Andijk)	
2010	<	0.06	<	0.056	13 (Brakel)	[12]
	<	<	<		3 (Keizersveer)	
	0.02	0.047	0.033	0.0461	12 (Lobith)	
	<	0.06	<	<	13 (Nieuwegein)	
	<	0.13	0.066	0.126	13 (Nieuwersluis)	
	<	<	<	<	13 (Andijk)	
	<	<	<		3 (Stellendam)	

The overall average of the 90^{th} percentile values of Brakel, Lobith and Nieuwersluis over 2010 is 0.08 µg/L. It is noted that the measured concentrations at Nieuwersluis are consistently higher than at the other sampling locations, the difference is about a factor of two.

In 2008, concentrations at nine locations in the Dommel area ranged from 0.09 to 0.68 µg/L.

Samples from the River Roer contained 0.24 and 0.27 µg/L in July and August 2009.

Concentrations in STP-effluents are 0.83 µg/L (average), 1.15 µg/L (90^{th} percentile), maximum is 2.4 µg/L (Waterdienst data).
Water board Rijnland reports concentrations in STP-influents in 2010 between 0.77 and 2.2 µg/L, the 90^{th} percentile is 1.95 µg/L. Effluent concentrations range from 0.62 to 2.1 µg/L, with a 90^{th} percentile of 2.05 µg/L.

21.8 Removal upon water treatment

Based on an estimated log K_{ow} of -1.89, VP of 5.05E-14 and BIOWIN3 value of 2.7099 (weeks to months), sotalol is considered difficult to remove by the current methods for surface water treatment. Reduction of the level of purification treatment will not be possible.

21.9 Environmental risk limits based on direct ecotoxicity

Regulatory standards or reliable proposals are not available. Sotalol is not included in the German ETOX database [44], US EPA Ecotox [39], and a quick scan for relevant papers in the open literature did not result in any useful references. The following data are available from the MistraPharma Database [89]:

Taxon	Species	L/EC_{50} Value [mg/L]	Remark	Reference
Bacteria	*Vibrio fischeri*	> 1000	30 min.	[89]
Algae	*Desmodesmus subspicatus*	> 3000	24 h	[89]
Crustacea	*Daphnia magna*	> 300	48 h	[89]

The data suggest that aquatic organisms are not particularly sensitive to sotalol. Because no data for fish are present, the base set (algae, *Daphnia*, fish) is not complete, and no ERL according to WFD-methodology can be derived. For derivation of an indicative MPC [13], an assessment factor of 3000 would be used in case acute data for two of the three base set species are available. This would lead to a value of 0.1 mg/L = 100 µg/L.

21.10 Environmental risk limits based on secondary poisoning

Not relevant.

21.11 Environmental risk limits based on human toxicology

21.11.1 Surface water for drinking water abstraction

A human toxicological threshold limit is not available. The recommended starting dose for adults is 80 mg, the common dose is 160 to 320 mg [4]. For other pharmaceuticals, the lowest therapeutic dose was used with an assessment factor of 100 to establish a provisional TL_{hh} [11]. For sotalol this would lead to a value of 1.6 mg per person per day.

Input: TL_{hh} = 1.6 mg per person, 2 L water per day, 10% of TL_{hh} allowed via drinking water. Since TL_{hh} is given per person, the correction for body weight that is normally applied for derivation of ERLs is not needed.
ERL (water for drinking water) = (1.6 x 0.1) / 2 = 0.08 mg/L = 80 µg/L.
If sotalol is proposed as drinking water relevant substance, this information should be checked by experts.

The proposed target value for pharmaceuticals according to the DMR-memorandum is 0.1 µg/L.

21.11.2 *Surface water for fish consumption*

Not relevant.

21.12 Summary and discussion

No regulatory standard or reliable proposal is available. Based on the available information, aquatic organisms seem to be relatively insensitive and an indicative MPC would be in the high µg/L range (> 100 µg/L). No human toxicological threshold limits are available either, a tentative TL_{hh} is derived on the basis of the recommended therapeutic dose. This results in a drinking water limit that is much higher than the target value as proposed by the drinking water companies of 0.1 µg/L. Monitoring data show the presence in surface water at relatively high levels at Nieuwersluis (0.11-0.16 µg/L), much lower levels are present at other locations (≈ 0.05 µg/L). Data from water boards indicate that higher levels may be found in smaller rivers.
The 90th percentile of concentrations in STP-effluents is 1.15-2.05 µg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.1-0.2 µg/L which is in accordance with measured data.
Based on the target value of 0.1 µg/L as proposed in the DMR-memorandum, and the average of the 90th percentile concentration in 2010 of 0.08 µg/L, the risk ratio is 0.8. The risk ratio based on ecotoxicity is <0.001.

ERL DMR-memorandum	0.1	µg/L
ERL direct ecotoxicity	> 100	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	80	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.08	µg/L
Risk ratio	0.8	ERL DMR
	0.001	ERL DW
	<0.001	ERL ECO

n.r. = not relevant

21.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- detected at three locations in 2007, 2009 and 2010, except for one location (Nieuwersluis), 90th percentile concentrations are lower than the DMR-target value; human-toxicological risk limit > DMR-target value;
- not relevant for ecology because the risk ratio is <0.01.

Recommendations

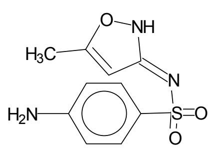
- continue monitoring;
- investigate high levels at Nieuwersluis.

22 Sulfamethoxazole

22.1 Introduction

Sulfamethoxazole is proposed by the RIWA as a drinking water relevant compound, because it is present in surface water used for drinking water abstraction. Furthermore, as a medicinal product it may rise public concern, and the potential development of resistance to antibiotics is seen as an important issue by drinking water experts. The risk of getting these compounds in drinking water is seen as damaging to the reputation of the drinking water companies.

22.2 Chemical identity

Name	Sulfamethoxazole
Chemical name	Benzenesulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl)-
CAS number	723-46-6
EC number	211-963-3
Molecular formula	C10H11N3O3S1
Molar mass	253.28
Structural formula	
SMILES code	Cc1cc(NS(=O)(=O)c2ccc(N)cc2)no1

22.3 Information on uses and emissions

Sulfamethoxazole is a sulfonamide bacteriostatic antibiotic against grampositive and gramnegative bacteria. Sulfonamides are structural analogs and competitive antagonists of para-aminobenzoic acid (PABA). They inhibit normal bacterial utilization of PABA for the synthesis of folic acid, an important metabolite in DNA synthesis. It is most often used as part of a synergistic combination with trimethoprim in a 5:1 ratio in co-trimoxazole, also known under trade names such as Bactrim, Septrin, or Septra; in Eastern Europe it is marketed as Biseptol. Its primary activity is against susceptible forms of *Streptococcus*, *Staphylococcus aureus* (including MRSA), *Escherichia coli*, *Haemophilus influenzae,* and oral anaerobes. It is commonly used to treat urinary tract infections. In addition it can be used as an alternative to amoxicillin-based antibiotics to treat sinusitis. It can also be used to treat toxoplasmosis.
In the Netherlands, 22 products containing sulfamethoxazole are registered, all in combination with trimethroprim [4]. The GIP-database does not contain use data on sulfamethoxazole [5]. The compound is not included in the Pollutant Release and Transfer Register [6].

22.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not applicable
REACH (1907/2006/EC)	Not registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	Not investigated
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Registered as pharmaceutical in NL D: Classified as water hazardous class 2 [14]

22.5 Existing or proposed water quality standards, risk limits etc.

Country	Value [µg/L]	Remark	Reference
NL	-		
CH	0.6	AA-EQS, NOEC *Synechococcus leopoliensis* with AF 10	[72]
CH	2.7	MAC-EQS, EC_{50} *S. leopoliensis* with AF 10	[72]
S	0.6	PNEC from industry MSDS; see CH	[28]
N	0.0268	PNEC, based on EC_{50} for *S. leopoliensis*; AF 1000	[27]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

22.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H315, 317, 319, 334, 335, 351, 361, 400, 410, 411	notified classification	[8]
log K_{ow}	0.48 0.89	estimated experimental	[72]
BCF	1.1 L/kg	estimated with log K_{ow} 0.89	[17]
Human toxicological threshold limit (TL_{hh})	0.13 mg/kg bw.d	60-d NOEAL 25 mg/kg bw.d; AF 200	[10]
	100 µg/kg milk	MRL set by EMEA based on 1.5 kg milk/day	[11]

22.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2005		0.11				170 data points; data from RIWA	[10]
2006	<	0.03	0.02	0.0164	0.03	11 (Andijk)	[12]
	0.01	0.03	*	0.0175	*	4 (Brakel)	
	<	0.06	0.03	0.0304	0.056	13 (Nieuwegein)	
	<	0.06	0.04	0.0342	0.056	13 (Nieuwersluis)	
2007	<	0.02	*	0.0112	*	4 (Brakel)	[12]
	<	0.06	0.02	0.0223	0.052	13 (Nieuwegein)	
	0.02	0.06	0.03	0.0338	0.056	13 (Nieuwersluis)	
	<	0.03	0.01	0.0146	0.026	13 (Andijk)	
2008	<	0.02	*	<	*	7 (Liège)	[12]
	<	0.025	*	<	*	4 (Heel)	
	<	0.03	*	0.0162	*	4 (Brakel)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
	<	0.057	*	0.025	*	9 (Keizersveer)	
	0.02	0.05	0.03	0.0338	0.046	13 (Nieuwegein)	
	<	0.04	0.03	0.0304	0.04	12 (Nieuwersluis)	
	<	0.02	0.02	0.0173	0.02	13 (Andijk)	
2009	<	0.03	*	0.017	*	5 (Liège)	[12]
	<	0.05	*	0.0237	*	4 (Brakel)	
	<	0.08	0.02	0.031	0.062	15 (Keizersveer)	
	<	0.05	0.03	0.0296	0.046	13 (Nieuwegein)	
	0.03	0.08	0.04	0.0446	0.076	13 (Nieuwersluis)	
	<	0.03	0.02	0.0188	0.03	13 (Andijk)	
2010	<	0.02	<	<	0.016	13 (Namêche)	[12]
	<	0.02	<	<	0.02	13 (Liège)	
	0.01	0.035	0.02	0.0192	0.033	13 (Brakel)	
	<	0.05	0.03	0.0292	0.046	13 (Keizersveer)	
	<	<	*	<	*	4 (Nieuwegein)	
	0.02	0.05	0.03	0.0315	0.0468	13 (Nieuwersluis)	
	0.012	0.03	0.02	0.0206	0.03	13 (Andijk)	
	0.01	0.04	0.025	0.025	0.037	12 (Stellendam)	

The overall average of the 90th percentile concentration in Dutch sampling points of the RIWA over 2010 is 0.03 µg/L.

During screening monitoring in 2003, the Water board De Dommel found concentrations of sulfamethoxazole between 0.02 and 0.37 µg/L.
In 2008, samples were taken at nine locations, seven of which showed concentrations of 0.02-0.05 µg/L which is comparable with the RIWA data. At two locations, higher levels were found (0.14 and 0.2 µg/L).

Samples from the River Roer contained 0.25 and 0.12 µg/L in July and August 2009.

Rademaker and De Lange [31] summarised monitoring data of pharmaceuticals in the Netherlands, based on an unpublished study by Verstraaten [32], RIWA reports from 2003, 2004 and 2005 and a RIZA report from 2003 [33]. Sulphamethoxazole was found in 109 out of 133 samples (82%), the highest concentration was 0.11 µg/L, the average was 0.028 µg/L.

In 2010, extracts of residues in passive samplers (POCIS and silicone rubbers) were tested for antibiotic activity using a plate counting method. In none of the samples sulphonamide activity was detected [34].

Concentrations in STP-effluents are 0.19 µg/L (average), 0.28 µg/L (90th percentile), maximum is 0.35 µg/L (Waterdienst data).

22.8 Removal upon water treatment

Based on a log K_{ow} of 0.48 VP of 1.30E-07 and BIOWIN3 value of 2.4297 (weeks to months), sulfamethoxazole is considered difficult to remove by simple surface water treatment, this is however not the case and sulfamethoxasole is removed 40-100% by UV treatment. Implementation of this technique implies that reduction of the level of purification treatment will not be possible.

22.9 Environmental risk limits based on direct ecotoxicity

For the present assessment, the AA-EQS of 0.6 µg/L (see section 22.5) is selected.

22.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

22.11 Environmental risk limits based on human toxicology

22.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.13 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.13 x 0.1 x 70) / 2 = 0.455 mg/L = 455 μg/L.

A provisional drinking water limit of 75 μg/L is reported in [11], based on the MRL in milk of 100 μg/kg. This MRL is based on a daily milk consumption of 1.5 kg per person, which leads to a tolerable daily intake of 150 μg/person d. With a daily water intake of 2 L, the equivalent concentration in water is 75 μg/L.

Depending on the human toxicological data, drinking water limits between 75 and 455 μg/L are derived. These values are all higher than the ecotoxicological risk limit of 0.6 μg/L and the proposed target value of 0.1 μg/L for pharmaceuticals according to the DMR-memorandum.

22.12 Surface water for fish consumption

Probably relevant because of H351, 361 (notified classification).

Input: TL_{hh} = 0.15 mg/person d, 115 g fish per day, 10% of TL_{hh} allowed via fish consumption, BCF = 1.1 L/kg.
ERL (food) = (0.15 x 0.1) / 0.115 = 0.13 mg/kg fish.
ERL (water) = 0.13 / 1.1 = 0.12 mg/L = 120 μg/L.

22.13 Summary and discussion

The ERLs for direct ecotoxicity of 0.6 μg/L as proposed in Switzerland are based on a thorough literature survey performed by known experts. Human toxicological risk limits depend on the input data and result in drinking water limits between 75 and 455 μg/L. These values are all higher than the ecotoxicological risk limit and much higher than the proposed target value of 0.1 μg/L for pharmaceuticals according to the DMR-memorandum.
Reliable monitoring data are available which show a consistent pattern. The overall average of the 90th percentile concentrations is 0.03 μg/L. Monitoring data from the Dommel area and River Roer show that concentrations in smaller water bodies may be higher.
The 90th percentile of concentrations in STP-effluents is 0.28 μg/L. Assuming a dilution factor of 10, estimated concentrations in surface water would be 0.03 μg/L which is in accordance with measured data.
Based on the average 90th percentile of measured concentrations of 0.03 μg/L and the ERL for direct ecotoxicity of 0.6 μg/L, the risk ratio is 0.05. Using the target value of 0.1 μg/L as proposed in the DMR-memorandum, the risk ratio is 0.3. Using the risk limits based on human toxicological data, the risk ratio is <0.001.

ERL DMR-memorandum	0.1	μg/L
ERL direct ecotoxicity	0.6	μg/L
ERL secondary poisoning	n.r.	μg/L
ERL drinking water	455 75	μg/L
ERL human fish consumption	120	μg/L
Environmental concentration	0.03	μg/L
Risk ratio	0.3	ERL DMR
	<0.001	ERL DW
	0.05	ERL ECO

n.r. = not relevant

22.14 Conclusion and recommendations

Relevance for drinking water production and ecology

- 90^{th} percentile concentrations are lower than the DMR-target value; concentrations in smaller water bodies may be higher;
- potentially relevant for ecology because the risk ratio is > 0.01.

Recommendation

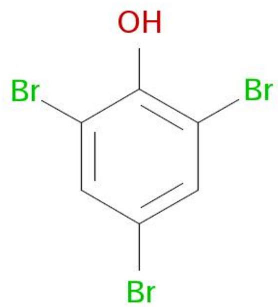
- continue monitoring.

23 2,4,6-Tribromophenol

23.1 Introduction

2,4,6-Tribromophenol is proposed by the Waterdienst as a potential relevant compound. It is used as a flame retardant and as a wood preservative. It was detected in surface waters and is selected for further screening based on its ecotoxicity [30]. It is included in the list of potential relevant substances in [100].

23.2 Chemical identity

Name	2,4,6-tribromophenol
Chemical name	
CAS number	118-79-6
EC number	204-278-6
Molecular formula	C6H3Br3O
Molar mass	330.8
Structural formula	
SMILES code	Brc1cc(Br)cc(Br)c1O

23.3 Information on uses and emissions

The following is cited from a WHO-evaluation [101]:
‘2,4,6-TBP is not used directly as a flame retardant, but rather as an intermediate for such products as end stop for brominated epoxy resin made from tetrabromobisphenol A (probably the largest application), tribromophenyl allyl ether, and 1,2-bis(2,4,6-tribromophenoxyethane) (Weil, 1993). The latter is prepared by the reaction of 2,4,6-TBP and ethylene in the presence of a base. It is the second most prevalent flame retardant used in acrylonitrile-butadiene-styrene resins (Weil, 1993). 2,4,6-TBP is reacted with sodium hydroxide to form the salt sodium tribromophenol in water, which is used as a wood preservative. Standard application methods of pressure and vacuum impregnation, dipping, brushing, and spraying of the wood are used. The solution is very effective in controlling insects, fungi, and bacteria in construction lumber, plywood timbers, railroad ties, fence posts, utility poles, landscape materials, and foundation materials (DSBG/BCL, personal communication, 2004). 2,4,6-TBP is registered as a wood preservative in South America; for example, the current pesticide register for Chile reveals that three products based on the sodium tribromophenol salt are approved for use as a fungicide treatment (two manufacturers in Chile and one in Brazil). However, it is not registered in the EU or USA and is not known to be registered in other parts of the world (DSBG/BCL, personal communication, 2004)’.

2,4,6-Tribromophenol is registered under REACH and the summary dossier is available via the ECHA-website [8]. The identified use according to the REACH dossier is manufacture of plastic products. It belongs to the following process categories: 14 ‘Production of preparations or articles by tabletting, compression, extrusion, pelletisation’, and environmental release category 4 ‘Industrial use of processing aids in processes and products, not becoming part of articles’. The market sector is PC 32 ‘Polymer preparations and compounds’, the sector of end

use is SU 12 ‘Manufacture of plastics products, including compounding and conversion’. According to the dossier, subsequent service life is not relevant for that use.
The compound is not included in the Pollutant Release and Transfer Register [6].

23.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not included in Annex I
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Not registered as biocide in NL

23.5 Existing or proposed water quality standards, risk limits et cetera

Country	Value [µg/L]	Remark	Reference
NL	-	-	-
EU	0.5	PNEC, AF 50 on NOEC 25 µg/L for *D. magna*	[8]
	2	PNEC, AF 50 on NOEC 0.1 mg/L for *D. magna*	[101]

23.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H301, 315, 317, 319, 361, 371, 373, 400, 410	notified classification	[8]
log K_{ow}	3.7 2.2 3.3	HPLC-method shake flask not spec.	[8]
BCF	120 L/kg	estimated	[101]
	20 L/kg	experimental; edible	[8,101,102]
	140 L/kg	experimental; viscera	
	83 L/kg	experimental; whole fish	
	513 L/kg	experimental	
Human toxicological threshold limit (TL_{hh})	0.25 mg/kg bw.d	oral DNEL for long-term systemic effects (general public)	[8]

23.7 Environmental concentrations

In 2009, 2,4,6-tribromophenol was detected two times during the screening monitoring by the Waterdienst, concentrations were 0.04 µg/L [30]. In 2010, it was detected four times during screening monitoring, concentrations were between 0.019 and 0.033 µg/L (Marcel Kotte, pers. comm.).

23.8 Removal upon water treatment

2,4,6-Tribromophenol is not put forward as a specific drinking water relevant substance by the RIWA.

23.9 Environmental risk limits based on direct ecotoxicity

Based on the summaries included in the REACH dossier, the PNEC of 0.5 µg/L as proposed by the registrant is derived in a correct way.

23.10 Environmental risk limits based on secondary poisoning

In the REACH-dossier [8], and assessments by OECD [102] and WHO [101], low birth weight and effects on viability of pups were noted at 1000 mg/kg bw.d in a reproduction study in which rats were exposed from 14 days before mating until day 3 of lactation. The next lower dose of 300 mg/kg bw.d is reported as the reproductive NOAEL. With a conversion factor of 20, this is equivalent to a NOEC of 6000 mg/kg fd. For this type of studies, an assessment factor of 90 is proposed, leading to PNECoral of 67 mg/kg fd. Using the BCF of 513 L/kg, the resulting PNECwater is 0.13 mg/L = 130 µg/L.
According to [101], there is no evidence for endocrine disruption.

23.11 Environmental risk limits based on human toxicology

23.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.25 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.25 x 0.1 x 70) / 2 = 0.875 mg/L = 875 µg/L.

Note that according to [101] it is not possible to derive reliable tolerable intakes for 2,4,6-tribromophenol for drinking water or food, since the only reported short-term toxicity study by the oral route is considered a screening test. The background of the derivation of the DNEL is not reported in the REACH-summary dossier.

For anthropogenic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

23.11.2 Surface water for fish consumption

Probably relevant because of H361 (notified classification).

Input: TL_{hh} = 0.25 mg/kg bw.d, 115 g fish per day, body weight 70 kg, 10% of TL_{hh} allowed via fish consumption, BCF = 513 L/kg.
ERL (food) = (0.25 x 0.1 x 70) / 0.115 = 15.2 mg/kg fish.
ERL (water) = 15.2 / 513 = 0.029 mg/L = 29 µg/L.

23.12 Summary and discussion

The lowest risk limit is the PNEC of 0.5 µg/L from the REACH-dossier. This PNEC is derived in a correct way. Based on an observed maximum concentration in freshwater in Japan of 0.3 µg/L, the WHO [101] calculated the PEC/PNEC ratio for 2,4,6-TBP as 0.15. Using the PNEC from REACH, the risk ratio would be 0.6. The WHO-assessment [101] states that 'it should be noted that the exposure information is extremely limited, and, thus, this risk factor should only be used with caution as a crude indicator. There were very limited production figures available and no release figures, and, therefore, modelling exposure concentrations was felt to be inappropriate at this stage.'
There are only few monitoring data for the Netherlands. Based on the highest measured concentration of 0.04 µg/L in 2009, the risk ratio is 0.08.

ERL DMR-memorandum	1	µg/L
ERL direct ecotoxicity	0.5	µg/L
ERL secondary poisoning	130	µg/L
ERL drinking water	875	µg/L
ERL human fish consumption	29	µg/L
Environmental concentration	max. 0.04	µg/L
Risk ratio	0.04	ERL DMR
	<0.001	ERL DW
	0.08	ERL ECO

n.r. = not relevant

23.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the DMR-target value;
- potentially relevant for ecology because the risk ratio is > 0.01, but this is based on limited monitoring data.

Recommendation

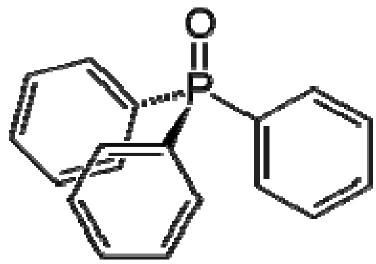
- continue screening monitoring by the Waterdienst.

24 Triphenylphosphine oxide

24.1 Introduction

Triphenylphosphine oxide is proposed by the Waterdienst as a potential relevant compound.

24.2 Chemical identity

Name	Triphenylphosphine oxide
Chemical name	Triphenyl-λ5-phosphanone
CAS number	791-28-6
EC number	212-338-8
Molecular formula	C18H15OP
Molar mass	278.29
Structural formula	
SMILES code	O=P(c(cccc1)c1)(c(cccc2)c2)c(cccc3)c3

24.3 Information on uses and emissions

Triphenylphosphine oxide is a by-product of many useful reactions in organic synthesis including the Wittig, Staudinger, and Mitsunobu reactions. It is also formed when triphenylphosphine dichloride is employed to convert alcohols into alkyl chlorides. The compound is not included in the Pollutant Release and Transfer Register [6].

24.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	

24.5 Existing or proposed water quality standards, risk limits et cetera

No information available.

24.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	H302, 315, 319, 335, 411, 412	notified classification	[8]
log K_{ow}	2.8	experimental	[8]
	2.83	experimental EpiSuite	[1]
BCF	51	calculated with log K_{ow} 2.83	[17]
Human toxicological threshold limit (TL_{hh})	0.008 mg/kg bw.d	based on NOEL 90 d dog test with AF 1000	[10]

24.7 Environmental concentrations

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2006	<	0.22	0.07	0.0823	0.15	104 (Nieuwegein)	[12]
	<	0.18	0.075	0.0857	0.175	14 (Nieuwersluis)	
	<	<		<		1 (Brakel)	
2007	<	<	<	<	<	29 (Brakel)	[12]
	<	0.183	<	<	0.103	106 (Nieuwegein)	
	<	<		<		4 (Andijk)	
2008	<	<		<		3 (Heel)	[12]
	<	<	<	<	<	28 (Brakel)	
	<	0.2	<	<	0.1	106 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<		<		4 (Andijk)	
2009	<	0.36	0.17	0.171	0.34	29 (Brakel)	[12]
	<	0.15	<	<	<	104 (Nieuwegein)	
	<	<	<	<	<	13 (Nieuwersluis)	
	<	<		<		4 (Andijk)	
2010	<	0.24	0.1	0.105	0.236	13 (Brakel)	[12]
	<	0.11	<	<	<	46 (Nieuwegein)	
	<	<	<	<	<	4 (Nieuwersluis)	
	<	<		<		1 (Andijk)	
	0.01	0.071	0.030	0.026	0.063	13 (Lobith); 3 <RG	Waterdienst data

Triphenylphosphine-oxide was detected during the screening monitoring by the Waterdienst over 2005-2009. In 2009, it was detected three times [30].

It is noted that from the RIWA-data it appears that before 2008 the compound was detected at Nieuwersluis and Nieuwegein, but not at Brakel. In 2009 and 2010, relatively high concentrations were detected at Brakel (average of 90th percentile 0.29 µg/L), but not at other locations. There is no obvious explanation for these observations.

Water board Roer and Overmaas provided monitoring data for 2008 (six locations) and 2009 (five locations). In 2008, triphenylphosphine-oxide was not detected at concentrations above the reporting limit of 0.02 µg/L. In 2009, the compound was detected occasionally at some locations, concentrations ranged from 0.02 to 0.04 µg/L.

24.8 Removal upon water treatment

Triphenylphosphine-oxide is not put forward as a specific drinking water relevant substance by the RIWA.

24.9 Environmental risk limits based on direct ecotoxicity

A PNEC is not derived in the REACH dossier. The following acute ecotoxicity data are available:

Taxon	Species	L/EC_{50} Value [mg/L]	Remark	Reference
Algae	*Scenedesmus subspicatus*	29.6	72 h growth rate	[8,9]
Crustacea	*Daphnia magna*	42.7	48 h	[8,9]
Mollusca	*Pomacea canaliculata*	12.2	72 h	[39]
Fish	*Leuciscus idus*	46-100	96 h	[8,9]
	Pimephales promelas	53.7	96 h	[9,39]

A 72-hours EC_{10} for algae of 9.8 mg/L is reported in the REACH dossier [8]. In the absence of chronic data for daphnids or fish, the PNEC may be derived by putting an assessment factor of 1000 on the lowest acute toxicity endpoint. This results in a PNEC of 12.2 µg/L.

24.10 Environmental risk limits based on secondary poisoning

Not relevant (BCF <100 L/kg).

24.11 Environmental risk limits based on human toxicology

24.11.1 Surface water for drinking water abstraction

A DNEL is not derived in the REACH dossier. The tentative TL_{hh} of 0.008 mg/kg bw.d of [10] is used.

Input: TL_{hh} 0.008 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.008 x 0.1 x 70) / 2 = 0.028 mg/L = 28 µg/L.

If triphenylphosphine-oxide is proposed as specific pollutant, the derivation of a human toxicological threshold limit should be checked, taking into account the information from the REACH dossier.

For anthropogenic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

24.11.2 Surface water for fish consumption

Not relevant (BCF <100 L/kg).

24.12 Summary and discussion

There are no accepted human toxicological threshold limits available, the available mammalian toxicity data may lead to a relatively low value. The risk limits based on direct ecotoxicity are also low, because chronic data are not available. In 2009 and 2010, relatively high concentrations were found at Brakel, the average of the 90^{th} percentile at that location is 0.29 µg/L. Using this concentration, the risk ratio based on the DMR-target value is 0.3. Using the drinking water limit based on human toxicological data, the risk ratio is 0.01. The risk ratio based on direct ecotoxicity is 0.02.

ERL DMR-memorandum	1	µg/L
ERL direct ecotoxicity	12.2	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	28	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.29	µg/L
Risk ratio	0.3	ERL DMR
	0.01	ERL DW
	0.02	ERL ECO

n.r. = not relevant

24.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the DMR-target value;
- potentially relevant for ecology because the risk ratio is > 0.01, but this is based on a conservative risk limit and monitoring data from one location only.

Recommendations

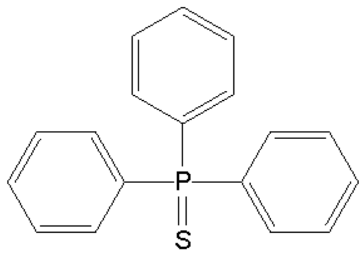
- continue monitoring;
- consult human toxicologist on the human toxicological threshold limit.

25 Triphenylphosphine sulfide

25.1 Introduction

Triphenylphosphine sulfide is proposed by the Waterdienst as a potential relevant compound.

25.2 Chemical identity

Name	Triphenylphosphine sulfide
Chemical name	Triphenyl-λ5-phosphanethione
CAS number	3878-45-3
EC number	223-407-7
Molecular formula	C18H15PS
Molar mass	294.357
Structural formula	
SMILES code	S=[P](C1=CC=CC=C1)(C2=CC=CC=C2)C3=CC=CC=C3

25.3 Information on uses and emissions

Triphenylphosphine-sulfide is used as an intermediate and as laboratory chemical. According to the information of Merck [103], the following uses are identified for triphenylphosphine-sulfide (description according to REACH):
SU 3 - Industrial uses: Uses of substances as such or in preparations at industrial sites.
SU 9 - Manufacture of fine chemicals.
SU 10 - Formulation [mixing] of preparations and/ or re-packaging (excluding alloys).

The following Process and Environmental release categories apply:
Process Categories

PROC1	Use in closed process, no likelihood of exposure.
PROC2	Use in closed, continuous process with occasional controlled exposure.
PROC3	Use in closed batch process (synthesis or formulation).
PROC4	Use in batch and other process (synthesis) where opportunity for exposure arises.
PROC5	Mixing or blending in batch processes for formulation of preparations and articles (multistage and/ or significant contact).
PROC8a	Transfer of substance or preparation (charging/ discharging) from/ to vessels/ large containers at non-dedicated facilities.
PROC8b	Transfer of substance or preparation (charging/ discharging) from/ to vessels/ large containers at dedicated facilities.
PROC9	Transfer of substance or preparation into small containers (dedicated filling line, including weighing).
PROC10	Roller application or brushing.
PROC15	Use as laboratory reagent.

Environmental Release Categories

ERC1	Manufacture of substances.

ERC2 Formulation of preparations.
ERC4 Industrial use of processing aids in processes and products, not becoming part of articles.
ERC6a Industrial use resulting in manufacture of another substance (use of intermediates).
ERC6b Industrial use of reactive processing aids.

In the evaluation of screening monitoring data over 2005-2009, triphenylphosphine sulfide is indicated as a biocide [30], but information on this use could not be found. The compound was detected in water after polishing/cleaning of plates treated with the anti-fouling paint Ecospeed in an experimental set-up [104]. According to one of the authors of the report, however, this has most likely been a coincidence and it is not likely that it originated from the paint. It might be possible that it is formed during the preparation of alkenes by organic synthesis (Rob Berbee, pers. comm.). The compound is not included in the Pollutant Release and Transfer Register [6].

25.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Pre-registered, deadline for submission of dossier 31/05/2013
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	

25.5 Existing or proposed water quality standards, risk limits et cetera

No information available.

25.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	R36,37,38	MSDS	[103]
	H302, 312, 315, 319, 335	notified classification	[8]
log K_{ow}	4.86	estimated; EpiSuite	[1]
BCF	2678 L/kg	estimated	[17]
Human toxicological threshold limit (TL_{hh})	not available		

25.7 Environmental concentrations

Triphenylphosphine-sulfide was detected during the screening monitoring by the Waterdienst over 2005-2009. In 2009, it was detected six times [30]. In 2010, it was detected seven times at Lobith, concentrations were between 0.01 and 0.034 µg/L, the average was 0.016 µg/L (Marcel Kotte, pers. comm.).

25.8 Removal upon water treatment

Triphenylphosphine-sulfide is not put forward as a specific drinking water relevant substance by the RIWA.

25.9 Environmental risk limits based on direct ecotoxicity

There are no ecotoxicity data available.

25.10 Environmental risk limits based on secondary poisoning

There are no mammal or bird toxicity values available. However, since the substance is self-classified in the MSDS, studies must have been performed.

25.11 Environmental risk limits based on human toxicology

25.11.1 Surface water for drinking water abstraction

There is no information on human toxicology.

25.11.2 Surface water for fish consumption

There is no information on human toxicology.

25.12 Summary and discussion

There are no human toxicological or ecotoxicological data available to evaluate the potential risks of triphenylphosphine-sulfide, while the compound is detected frequently.

ERL DMR-memorandum	1	µg/L
ERL direct ecotoxicity	?	µg/L
ERL secondary poisoning	?	µg/L
ERL drinking water	?	µg/L
ERL human fish consumption	?	µg/L
Environmental concentration	0.29	µg/L
Risk ratio	0.3	ERL DMR
	?	ERL ECO

25.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the DMR-target value;
- relevance for ecology unknown, since ecotoxicity data are not available.

Recommendations

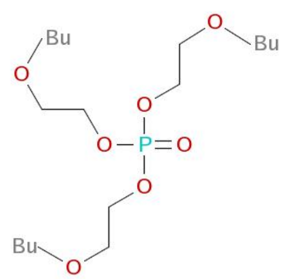
- continue monitoring;
- postpone evaluation until information becomes available via REACH.

26 Tris(2-butoxyethyl) phosphate (TBEP)

26.1 Introduction

TBEP is proposed by the Waterdienst as a potential relevant compound, because diffuse emissions may be expected in view of the use as softener.

26.2 Chemical identity

Name	Tris(2-butoxyethyl) phosphate
Chemical name	2-butoxyethanol phosphateKronitex KP-140; KP-140Phosflex T-BEP; Phosflex 176C; Amgard TBEPTBOP; TBEP; TBXPtri(2-butoxyethanol)phosphatetri(2-butylethylether) phosphatetributoxyethyl phosphatetributyl cellosolve phosphatetris(2-n-butoxyethyl)phosphatetris(butylglycol) phosphate
CAS number	78-51-3
EC number	201-122-9
Molecular formula	C18H39O7P
Molar mass	398.54
Structural formula	
SMILES code	=P(OCCOCCCC)(OCCOCCCC)OCCOCCCC

26.3 Information on uses and emissions

TBEP is used mainly as self levelling agent in floor polishes. Further TBEP is used as solvent in some resins, as viscosity modifier in plastisols, as antifoam and also as a plasticizer in synthetic rubber, plastics and lacquers (IPCS, 2000, cited in [105]). TBEP is not considered a flame retardant and is not used in plastisols and plastic ware applications [105]. The compound is not included in the Pollutant Release and Transfer Register [6].

26.4 Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not included
Existing Substances Reg. (793/93/EC)	Not included
REACH (1907/2006/EC)	Registered
Substances of Very High Concern (1907/2006/EC)	No
Pesticides (91/414 EEC; 1107/2009/EC)	Not applicable
Biocides (98/8/EC)	Not applicable
PBT substances	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	

26.5 Existing or proposed water quality standards, risk limits etc.

Country	Value [µg/L]	Remark	Reference
NL	13	MPC valid for dissolved and total concentrations; refers to direct ecotoxicity	[49]

26.6 Secondary poisoning and human toxicology

Parameter	Value	Remark	Reference
Classification	R66, 67		[9]
	H312, 315, 319, 332, 335	notified classification	[8]
log K_{ow}	3.75	experimental	[105]
	3.65	experimental	
	4.02	estimated	
	3.0	estimated	
BCF	6 L/kg	experimental	[8]
	307 L/kg	estimated	[17]
Human toxicological threshold limit (TL_{hh})	0.25 mg/kg bw.d	oral DNEL for general population	[8]
	0.2 mg/kg bw.d	provisional oral minimal risk level	[106]

26.7 Environmental concentrations

Monitoring data for TBEP in surface water and STP-effluents are cited in [105]. In 2002, the 90th percentile concentration of TBEP at Nieuwegein was 0.32 µg/L (range 0.16-0.40, average 0.22 µg/L).

In 2010, TBEP was included in the screening monitoring by the Waterdienst at Lobith. It was detected above the reporting limit in one out of 13 samples, the concentration was 0.1 µg/L (Marcel Kotte, pers. comm.).

Water board Roer and Overmaas provided monitoring data. In 2009, TBEP was not detected above the reporting limit , except for one occasion when 0.03 µg/L was measured. Data for 2010 are summarised below, TBEP was detected in 7 out of 12 monthly samples.

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark
2010	<0.02	0.82		0.10*	0.11*	12 (Roer)
	<0.02	0.03				5 (Anselderbeek)
	<0.02	0.12				4 (Worm)

* half of the reporting limit used in case of non-detects

The range of concentrations in five STP-effluents in the Meuse basin was 0.05 to 1.12 µg/L. STP-effluents taken in Friesland at the end of the 1990's contained 2 µg/L maximum [105].

26.8 Removal upon water treatment

TBEP is not put forward as a specific drinking water relevant substance by the RIWA.

26.9 Environmental risk limits based on direct ecotoxicity

An $MPC_{eco, water}$ of 13 µg/L was derived in [105] by putting an assessment factor of 1000 to the LC_{50} of 13 mg/L for *Pimephales promelas*. Data on algae were missing. An algae study is included in the REACH-summary dossier [8], the EC_{50} for growth rate is 61 mg/L and the NOEC is
7.6 mg/L. These additional endpoints do not influence the height of the

assessment factor and the resulting PNEC. The $MPC_{eco,\ water}$ of 13 µg/L is used for the present evaluation.

26.10 Environmental risk limits based on secondary poisoning

Not considered relevant by Verbruggen et al. (2005).

26.11 Environmental risk limits based on human toxicology

26.11.1 Surface water for drinking water abstraction

Input: TL_{hh} = 0.2 mg/kg bw.d, 2 L water per day, body weight 70 kg, 10% of TL_{hh} allowed via drinking water.
ERL (water for drinking water) = (0.2 x 0.1 x 70) / 2 = 0.700 mg/L = 700 µg/L.

For anthropogenic compounds without a known specific action, the target value as proposed by the DMR-memorandum is 1 µg/L.

26.11.2 Surface water for fish consumption

Not considered relevant [105].

26.12 Summary and discussion

The current water quality standard for TBEP is 13 µg/L, based on direct ecotoxicity. It is derived using a high assessment factor, since only acute data are available. Secondary poisoning is not relevant, and risk limits for abstraction of drinking water are not critical. The comppound was found regularly in the River Roer, but only once at Lobith.

MKN direct ecotoxicity	13	µg/L
ERL DMR-memorandum	1	µg/L
ERL secondary poisoning	n.r.	µg/L
ERL drinking water	700	µg/L
ERL human fish consumption	n.r.	µg/L
Environmental concentration	0.11	µg/L
Risk ratio	0.1	DMR
	0.008	ECO

n.r. = not relevant

26.13 Conclusion and recommendations

Relevance for drinking water production and ecology

- not put forward by the RIWA, and measured concentrations are lower than the DMR-target value;
- not relevant for ecology, because the risk ratio is <0.01 and the compound is detected only occasionally in larger water bodies.

Recommendation

- continue monitoring.

References

1. US EPA. 2011. EpiSuite version 4.10, January 2011.
2. ICPR/ICBR. 2011. Rijnstoffenlijst 2011. Koblenz, Germany. International Commission for the Protection of the Rhine/Internationale Commissie ter Bescherming van de Rijn. Report nr. 189. http://www.iksr.org/uploads/media/189_nl.pdf.
3. ICPR/ICBR. 2011. Evaluatiereport röntgencontrastmiddelen. Koblenz, Germany. International Commission for the Protection of the Rhine/Internationale Commissie ter Bescherming van de Rijn. Report nr. 187.
4. CBG. 2011. College ter beoordeling van geneesmiddelen. http://www.cbg-meb.nl/CBG/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/default.htm. Accessed December 2011.
5. CVZ. 2011. GIPdatabank: informatie over genees- en hulpmiddelen. College voor Zorgverzekeringen http://www.gipdatabank.nl/index.asp?scherm=homepage&infoType=a. Accessed November 2011.
6. PRTR. 2011. Pollutant Release and Transfer Register (Emissie Registratie) www.emissieregistratie.nl. Accessed October 2011.
7. IAWR/IAWD/RIWA. 2008. Danube, Meuse and Rhine memorandum 2008.
8. ECHA. 2012. European Chemicals Agency. Information on chemicals. http://echa.europa.eu/web/guest/information-on-chemicals. Accessed March 2012.
9. ESIS. 2012. European chemical Substances Information System http://ecb.jrc.ec.europa.eu/esis/. Accessed November 2011.
10. Schriks M, Heringa MB, Van der Kooi MME, De Voogt P, Van Wezel AP. 2010. Toxicological relevance of emerging contaminants for drinking water quality. Wat Res 44, 461-476.
11. Versteegh JFM, Van der Aa NGFM, Dijkman E. 2007. Geneesmiddelen in drinkwater en drinkwaterbronnnen. Resultaten van het meetprogramma 2005/2006. Bilthoven, the Netherlands. RIVM. Report nr. 703719016 (in Dutch).
12. RIWABase. 2011. Water Quality Database of the Association of River Waterworks, the Netherlands.
13. Van Herwijnen R, Janssen PJCM, Haverkamp THA, De Poorter LRM. 2009. Handreiking voor de afleiding van indicatieve milieurisicogrenzen (Interimversie 2009). Bilthoven, the Netherlands. RIVM. Report nr. 601782025 (in Dutch).
14. Umweltbundesamt. 2000. Wassergefährdende Stoffe.
15. Oekotoxzentrum. 2010. Stoffdatenblattentwurf für Benzotriazol (Stand 12/03/2010, update 10/05/10).
16. MERCK. 2011. http://www.merckmillipore.com/germany/chemicals/. Accessed October 2011.
17. Veith GD, Defoe DL, Bergstedt BV. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J Fish Res Board Can 36, 1040-1048.
18. Loos R, Gawlik BM, Locoro G, Rimaviciute E, Contini S, Bidoglio G. 2009. EU-wide survey of polar organic persistent pollutants in European river waters. Env Pollut 157, 561-568.
19. EC. 2010. BISPHENOL-A CAS No: 80-05-7 EINECS No: 201-245-8 RISK ASSESSMENT. Complete risk assessment in one document (February 2010). http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/bisphenolareport325.pdf.
20. SCENIHR. 2012. Request for a scientific opinion on the safety of the use of Bisphenol A in medical devices. Scientific Committee on Emerging and

newly Identified Health Risks. http://ec.europa.eu/health/scientific_committees/consultations/calls/scenihr_call_info_11_en.htm.
21. EFSA. 2008. Scientific Opinion of the Panel on Food additives, Flavourings, Processing aids and Materials in Contact with Food (AFC) on a request from the Commission on the toxicokinetics of Bisphenol A. The EFSA Journal 759, 1-10.
22. Waterbase. 2011. www.waterbase.nl. Accessed October 2011.
23. Van der Aa NGFM, Kommer GJ, De Groot GM, Versteegh JFM. 2008. Geneesmiddelen in bronnen voor drinkwater. Monitoring, toekomstig gebruik en beleidsmaatregelen. Bilthoven, the Netherlands. RIVM. Report nr. 609715002 (in Dutch).
24. Oekotoxzentrum. 2010. Stoffdatenblattentwurf für Carbamazepin (Stand 15/02/2010; update 30/04/2010).
25. INÉRIS. 2011. Normes de qualité environnementale. CARBAMAZEPINE – N° CAS : 298-46-4. DRC-11-112070-04500A. http://www.ineris.fr/substances/fr/.
26. EC. 2010. Draft EQS dossier prepared for carbamazepine in the context of selection of priority and priority hazardous substances under the WFD. Available via http://www.reseau.eaufrance.fr/webfm_send/1241.
27. Grung M, Heimstad ES, Moe M, Schlabach M, Svenson A, Thomas K, Wodegiorgis A. 2007. Human and veterinary pharmaceuticals, narcotics, and personal care products in the environment. Current state of knowledge and monitoring requirements. Statens forurensningstilsyn. Report nr. 2325/2007.
28. FASS. 2011. www.fass.se. Accessed November 2011.
29. Van der Aa NGFM, P.L.A. VV, Van Leeuwen LC, Post M. 2011. Assessment of potential risks of 11 pharmaceuticals for the environment. Using environmental information from public databases. Bilthoven, Nederland. RIVM. Report nr. 601711003.
30. Grontmij | Aquasense. 2010. Evaluatie screening RWS (2005 – 2009). Aanbevelingen wat betreft gewasbeschermingsmiddelen en farmaceutica. Lelystad, the Netherlands. Rijkswaterstaat/Waterdienst. Report nr. 275456.
31. Rademaker W, De Lange M. 2009. De risico's van geneesmiddelen in het aquatisch milieu. H2O 5, 29-32.
32. Verstraaten M. 2008. Gezond watermilieu. Onderzoek naar het voorkomen en de risico's van medicijnen in het watermilieu en mogelijk te nemen maatregelen. Master Thesis Twente University. http://essay.utwente.nl/58113/1/scriptie_M_Verstraaten.pdf.
33. Schrap SM, Rijs GBJ, Beek MA, Maaskant JFN, Staeb J, Stroomberg G, Tiesnitsch J. 2003. Humane en veterinaire geneesmiddelen in Nederlands oppervlaktewater en afvalwater. Een screening in 2002. Lelystad, the Netherlands. RIZA. Report nr. 2003.023 (in Dutch).
34. Van der Oost R, Nguyen MT. 2011. Passive sampling 2010; Onderzoek naar de oppervlaktewaterkwaliteit in het Waternet beheersgebied met passieve bemonstering. Waternet. Report nr. 11.035464 (in Dutch).
35. Besluit kwaliteitseisen en monitoring water 2009. Staatsblad 2010 (15).
36. HSDB. 2011. Hazardous Substances Database. http://toxnet.nlm.nih.gov/index.html. Accessed December 2011.
37. Thomas KV, Thain JE, Waldock MJ. 1999. Identification of toxic substances in United Kingdom estuaries. Environ Toxicol Chem 18, 401-411.
38. Office of Pesticide Programs. 2011. Ecotox Database. http://www.ipmcenters.org/Ecotox/. Accessed December 2011.
39. US EPA. 2011. Ecotox database. http://cfpub.epa.gov/ecotox/quick_query.htm. Accessed October 2011.
40. OECD. 2011. Ecological Categorization Results from the Canadian Domestic Substance List.

http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=1A5954E6-28DE-470A-866B-9E1F62714511. Accessed October 2011.
41. US EPA. 1994. Registration Eligibility Dossier Chloroxylenol. http://www.epa.gov/oppsrrd1/REDs/3045.pdf.
42. Ctgb. 2011. Bestrijdingsmiddelendatabank. Wageningen, the Netherlands. College voor de toelating van gewasbeschermingsmiddelen en biociden.
43. EC. 2010. N,N- diethyl-meta-toluamide (DEET) (PT 19). Assessment report Finalised in the Standing Committee on Biocidal Products at its meeting on 11 March 2010 in view of its inclusion in Annex I or IA to Directive 98/8/EC. http://ecb.jrc.ec.europa.eu/documents/Biocides/ANNEX_I/ASSESSMENT_REPORTS/AnnexI_AR_134-62-3_PT19_en.pdf.
44. ETOX. 2011. Information System Ecotoxicology and Environmental Quality Targets. http://webetox.uba.de/webETOX/. Accessed December 2011.
45. Verhagen FT, De Coninck L, Vervest F. 2008. Brede screening bestrijdingsmiddelen Maasstroomgebied. Den Bosch, the Netherlands. Royal Haskoning Nederland. Report nr. 9T3398/R00002/902173/AH/DenB (in Dutch).
46. EC. 2010. Draft dossier prepared for dichlofluanid in the context of selection of priority and priority hazardous substances under the WFD. Available via http://www.reseau.eaufrance.fr/webfm_send/1247.
47. EC. 2006. Directive 98/8/EC concerning the placing of biocidal products on the market. Inclusion of active substances in Annex I to Directive 98/8/EC. Assessment report dichlofluanid. Pt 8. http://esis.jrc.ec.europa.eu/doc/biocides/annex_I/assessment_reports/AnnexI_AR_1085-98-9_PT08_en.pdf.
48. Helpdesk Water. 2011. Zoeksysteem normen voor het waterbeheer.
49. RIVM. 2011. Risico's van Stoffen. http://www.rivm.nl/rvs/. Accessed October 2011.
50. RIWA. 2010. Jaarrapport 2010 De Rijn. Nieuwegein, the Netherlands. Association of River Waterworks.
51. De Rijk S, Van den Berg G, Puijker L. 2009. Nieuwe ontwikkelingen in het Maasstroomgebied; Drinkwater in het stroomgebiedbeheerplan Maas. Nieuwegein, the Netherlands. KWR Watercycle Research Institute. Report nr. 09.002 (in Dutch).
52. Stein A. 2009. Antifouling biociden in oppervlaktewater. Methodeontwikkeling, validatie en screening. Lelystad, the Netherlands. Rijkswaterstaat Report nr. 2009WGML31x (in Dutch).
53. Ctgb. 2007. Collegebesluit (Her)beoordelig niet geprioriteerde gewasbeschermingsmiddelen en biociden Chloorrubber Antifouling 2000, 10692 N. 1 oktober 2007. http://www.ctb.agro.nl/ctb_files/10692N_25d.html.
54. RIVM. 2007. Afleiden van indicatieve milieukwaliteitsnormen voor 2-chloorallylalcohol, 2,3-dichloorhydrine, difenylolmethaan, glycerine, glycidol, isopropylether, MIBK, monochloorhydrine, trimethylammoniumchloride. Internal report prepared for RIZA, 16 March 2007.
55. EC. 2002. European Union Risk Assessment Report 1,4-DIOXANE CAS No: 123-91-1 EINECS No: 204-661-8 RISK ASSESSMENT. http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/dioxanereport038.pdf.
56. Janssen P. 1997. Ad-hoc advies 1,4-dioxaan. Bilthoven, the Netherlands. RIVM. Internal report 05484A00.
57. US EPA. 2010. Integrated Risk Information System. 1,4-Dioxane (CASRN 123-91-1).
58. EC. 2008. European Union Risk Assessment Report. 1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYLCYCLOPENTA-γ-2-BENZOPYRAN (1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYLIN-DENO[5,6-

C]PYRAN – HHCB CAS No: 1222-05-5 EINECS No: 214-946-9 RISK ASSESSMENT Final version, May 2008. http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/hhcbreport414.pdf.
59. De Boer R, Staeb J. 2004. Vergeten stoffen 2003; screeningsonderzoek in oppervlaktewater en afvalwater. Prioritering volgens EU methodiek COMMPS Lelystad, the Netherlands. Rijkswaterstaat/Waterdienst. Report nr. W2004.177X (in Dutch).
60. Liebig M, Alonso Fernandez A, Blübaum-Gronau E, Boxall A, Brinke M, et al. 2010. Environmental risk assessment of Ivermectin: A case study IEAM 6, 567-587.
61. Jongbloed RH, Blankendaal VG, Kan CA, Van Dokkum HP, Bernhard R, Rijs GBJ. 2001. Milieurisico's van diergeneesmiddelen en veevoederadditieven in Nederlands oppervlaktewater; een verkennende studie. Apeldoorn, the Netherlands. TNO Milieu, Energie en Procesinnovatie. Report nr. TNO-MEP– R 2001/472 (in Dutch).
62. JECFA. 2002. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. Ivermectin.
63. Boxall ABA, Fogg LA, Baird DJ, Lewis C, Telfer TC, Kolpin D, Gravell A, Pemberton E, Boucard T. 2007. Targeted monitoring study for veterinary medicines in the environment. Bristol, United Kingdom. Environment Agency. Report nr. SC030183.
64. Fernández C, Porcel MA, Alonso A, San Andrés M, Tarazona JC. 2011. Semi-field assessment of the run-off potential and environmental risk of the parasiticide drug ivermectin under Mediterranean conditions Environ Sci Pollut Res 18, 1194-1201.
65. Montforts MHMM, Van Rijswick HFMW, Udo de Haes HA. 2004. Legal constraints in EU product labelling to mitigate the environmental risk of veterinary medicines at use. Reg Toxicol Pharmacol 40, 327-335.
66. Sanderson H, Laird B, Pope L, Brain R, Wilson C, Johnson D, Bryning G, Peregrine AS, Boxall A, Solomon K. 2007. Assessment of the environmental fate and effects of ivermectin in aquatic mesocosms. Aquat Toxicol 85, 229-240.
67. Montforts MHMM, Keessen A. 2007. Openbaarheid van milieu-informatie bij registratie van (dier)geneesmiddelen. Bilthoven, the Netherlands. RIVM. Report nr. 6015000006 (in Dutch).
68. IPCS. 2011. INCHEM. Chemical Safety Information from Intergovernmental Organizations. International Programme on Chemical Safety. http://www.inchem.org/documents/jecfa/jeceval/jec_1284.htm.
69. Isidori M, Lavorgna M, Nardelli A, Pascarella L, Parrella A. 2005. Toxic and genotoxic evaluation of six antibiotics on non-target organisms Sci Total Environ 346, 87-98.
70. Besse J-P, Garric J. 2007. Médicaments à usage humain: risque d'exposition et effets sur les milieux récepteurs. Lyon, France. Cémagref.
71. Cleuvers M. 2003. Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects Toxicol Letters 142, 185-194.
72. Oekotoxzentrum. 2011. Stoffdatenblattentwurf für Metoprolol (Stand 23/07/2010, Einarbeitung des Gutachtens am 09/09/2011).
73. VROM. 2007. Uitvoeringsprogramma diffuse bronnen waterverontreiniging. Den Haag, the Netherlands. Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.
74. EC. 2002. European Union Risk Assessment Report TERT-BUTYL METHYL ETHER CAS No: 1634-04-4 EINECS No: 216-653-1 RISK ASSESSMENT. http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/mtbereport313.pdf.
75. Swartjes FA, Baars AJ, Fleuren RHLJ, Otte PF. 2004. Risicogrenzen voor MTBE (Methyl tertiair-Butyl Ether) in bodem, sediment, grondwater,

oppervlaktewater, drinkwater en voor drinkwaterbereiding. Bilthoven, the Netherlands. RIVM. Report nr. 711701039 (in Dutch).
76. DK EPA. 2007. Factsheet oxytetracycline and oxytetracycline hydrochloride Kopenhagen, Denmark. Danish Environmental Protection Agency. (Quality standards published in Statutory order 1022: Bekendtgørelse om miljøkvalitetskrav for vandområder og krav til udledning af forurenende stoffer til vandløb, søer eller havet).
77. DK EPA. 2011. http://www.mst.dk/English/Chemicals/Substances_and_materials/The_advisory_list_for_selfclassification/CLPclassification.htm. Accessed November 2011.
78. JECFA. 2002. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. Oxytetracycline.
79. EMEA. 1995. Committee for veterinary medicinal products. Oxytetracycline, tetracycline, chlortetracycline. EMEA/MRL/023/95. http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500015378.pdf.
80. Montforts MHMM, Rijs GBJ, Staeb JA, Schmitt H. 2007. Diergeneesmiddelen en natuurlijke hormonen in oppervlaktewater van gebieden met intensieve veehouderij. Bilthoven, the Netherlands. RIVM. Report nr. 601500004 (in Dutch).
81. Schilt R, Van de Lagemaat D. 2009. Rapportage deelresultaten project Antibiotica in de bodem. Deelrapport: Antibiotica in de bodem: Onderzoek van grondwater, bodem en mest SKB projectnummer: PP8348 (in Dutch).
82. Kools SAE, Kuiper MW, Roorda JH, Derksen JGM. 2009. Verg(h)ulde pillen. Case studie LUMC te Leiden. Utrecht, the Netherlands. STOWA. Report nr. 2009-W02 (in Dutch).
83. Kuiper MW, Kools SAE, Roorda JH, Derksen JGM. 2009. Verg(h)ulde pillen. Case studie Refaja ziekenhuis te Stadskanaal. Utrecht, the Netherlands. STOWA. Report nr. 2009-W01 (in Dutch).
84. Kuiper MW, Roorda JH, Kools SAE, Derksen JGM. 2009. Verg(h)ulde pillen. Case studie Antonius ziekenhuis te Nieuwegein. Utrecht, the Netherlands. STOWA. Report nr. 2009-W03 (in Dutch).
85. Yang S, Carlson K. 2004. Routine monitoring of antibiotics in water and wastewater with a radioimmunoassay technique. Wat Res 38, 3155-3166.
86. Vazquez-Roig P, Andreu V, Onghena M, Blasco C, Picó Y. 2011. Assessment of the occurrence and distribution of pharmaceuticals in a Mediterranean wetland (L'Albufera, Valencia, Spain) by LC-MS/MS. Anal Bioanal Chem 400, 1287-1301.
87. Bergmann A, Fohrmann R, Weber F-A. 2011. Zusammenstellung von Monitoringdaten zu Umweltkonzentrationen von Arzneimitteln. Dessau-Roßlau, Germany. Umweltbundesamt. Report nr. 66/2011.
88. Jones OAH, Voulvoulis N, Lester JN. 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. Wat Res 36, 5013-5022.
89. Mistra. 2011. MistraPharma. Sweden, Stockholm: Swedish Foundation for Strategic Environmental Research. http://www.wikipharma.org/welcome.asp. Accessed October 2011.
90. Ando T, Nagase H. 2007. A novel method using cyanobacteria for ecotoxicity test of veterinary antimicrobial agents. Environ Toxicol Chem 26, 601-606.
91. Hanson ML, Knapp CW, Graham DW. 2006. Field assessment of oxytetracycline exposure to the freshwater macrophytes Egeria densa Planch. and Ceratophyllum demersum L. Environ Pollut 141, 434-442.
92. Martindale. 2011. Martindale: The Complete Drug Reference. http://www.medicinescomplete.com/mc/martindale/current/.

93. CVZ. 2011. Farmacotherapeutisch Kompas. College voor Zorgverzekeringen http://www.fk.cvz.nl/.
94. IUCLID. 2000. Dataset phenazone. http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/60800.pdf.
95. CBS. 2011. Centraal Bureau voor de Statistiek. http://www.cbs.nl/nl-NL/menu/themas/natuur-milieu/cijfers/default.htm. Accessed November 2011.
96. EC. 2007. Directive 98/8/EC concerning the placing of biocidal products on the market. Inclusion of active substances in Annex I to Directive 98/8/EC. Assessment report propiconazole. Product-type 8 (Wood preservatives). http://esis.jrc.ec.europa.eu/doc/biocides/annex_I/assessment_reports/AnnexI_AR_60207-90-1_PT08_en.pdf.
97. EC. 2003. Review report for the active substance propiconazole. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 15 April 2003 in view of the inclusion of propiconazole in Annex I of Directive 91/414/EEC. http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1-51_en.pdf.
98. Schrap SM, Tiesnitsch J, Staeb J. 2006. Bestrijdingsmiddelenscreening in de rijkswateren. Honderden bestrijdingsmiddelen in 2005. Lelystad, the Netherlands. RIZA Report nr. 2006.020 (in Dutch).
99. EC. 2007. Review report for the active substance propyzamide finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 26 February 2003 in view of the inclusion of propyzamide in Annex I of Directive 91/414/EEC. http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1-33_en.pdf.
100. Van Wezel AP, Kalf D. 2000. Selection of substances deserving policy attention. Bilthoven, the Netherlands. RIVM. Report nr. 601503017.
101. WHO. 2005. Concise International Chemical Assessment Document 66. 2,4,6-Tribromophenol and other simple brominated phenols. Geneva, Switzerland. World Health Organization.
102. OECD. 2005. SIDS Initial assessment report 2,4,6-tribromophenol. CAS 118-79-6. http://www.chem.unep.ch/irptc/sids/OECDSIDS/118796.pdf.
103. MERCK. 2010. Materials Safety Datasheet triphenylphosphine-sulfide. Available via http://www.merck-chemicals.com/netherlands/triphenylphosphine-sulfide/MDA_CHEM-841711/p_uuid?attachments=MSDS.
104. Wijga A, Erdtsieck E, Romeijn J, Berbee R, Tiesnitsch J, Rotteveel S, Eibrink L. 2008. Biocidevrije 'antifouling' voor schepen Emissies vanuit de onderwater coating 'Ecospeed' (in Dutch). Lelystad, the Netherlands. Rijkswaterstaat/Waterdienst. Report nr. 2008.057.
105. Verbruggen EMJ, Rila JP, Traas TP, Posthuma-Doodeman CJAM, Posthumus R. 2005. Environmental Risk Limits for several phosphate esters, with possible application as flame retardant. Bilthoven, the Netherlands. RIVM. Report nr. 601501024.
106. ITER. 2011. International Toxicity Estimates of Risk. http://www.tera.org/ITER/index.html. Accessed December 2011.

Dit is een uitgave van:

Rijksinstituut voor Volksgezondheid en Milieu
Postbus 1 | 3720 BA Bilthoven
www.rivm.nl