Dealing with pharmaceuticals in drinking water production

Occurrence in drinking water (sources) and removal efficiency of treatment techniques

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KWR Watercycle Research Institute

BTO

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Preface

Pharmaceuticals can enter the environment, and thus be found in drinking water sources. As a result they potentially may end up in drinking water in low concentrations. Within the framework of BTO the project 'dealing with pharmaceuticals in drinking water production' was formulated. In this project a risk assessment was carried out and risk management options for pharmaceuticals and their metabolites in drinking water production were investigated. This project covered two research topics, assigned to the KWR research groups 'Water Treatment' (WT) and 'Chemical Water Quality' (CW). The objective of the research theme assigned to CW was to relate the environmental concentrations of pharmaceuticals to their consumption, and to screen Dutch surface waters and drinking water for the presence of pharmaceuticals and their transformation products. The study included a first inventory of veterinary pharmaceuticals. A human health risk assessment of pharmaceuticals and their metabolites was carried out. Two selections of pharmaceuticals were made, one for screening of human health risks, and one for research with three different drinking water treatment techniques. The objective for WT was to study these treatment techniques, in order to determine the most efficient and sustainable approach to deal with pharmaceuticals in drinking water production. Various existing drinking water treatment methodologies (active carbon filtration, UV/hydrogen peroxide oxidation with Low pressure UV lamps, and membrane filtration) are assessed in terms of removal efficiency for pharmaceuticals and their metabolites. The results of all individual research topics were reported in separate reports and papers:

- Thomas ter Laak, Monique van der Aa, Corine Houtman, Peter stoks, Annemarie van Wezel; Temporal and spatial trends of pharmaceuticals in the Rhine; RIWA report; Feb. 2010
- T.L. ter Laak, M. van der Aa, C.J. Houtman, P.G. Stoks, A.P. van Wezel; Relating environmental concentrations of pharmaceuticals to consumption: a mass balance approach for the river Rhine; Environ. Int. 36(5), 403-409; 2010
- Thomas ter Laak, Leo Puijker, Annemarie van Wezel; Veterinary Pharmaceuticals in drinking water sources; a first inventory; Nov. 2010
- Thomas ter Laak; Wetgeving voor Diergeneesmiddelen en de relevantie voor de watersector; notitie; Dec. 2010
- Thomas ter Laak, Bas Hofs, Cindy de Jongh, Bas Wols, Roberta Hofman-Caris; Selecting relevant pharmaceuticals and metabolites for monitoring, risk assessment and removal efficiency studies; BTO 2011.100 (s), July 2011
- Thomas ter Laak; Mobility of antibiotic resistance genes in the environment and potential threats for drinking water; BTO 2012.022; Aug. 2012
- Cindy de Jongh, Pascal Kooij, Thomas ter Laak; Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water; BTO 2011.045, Nov. 2011
- C.M. de Jongh, P.J.F. Kooij, P. de Voogt, T.L. ter Laak; Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water; Sci. Tot. Environm. 427-428, 70-77, 2012
- T. ter Laak, P. Kooij; Screening for pharmaceuticals and metabolites in groundwater; BTO 2012.227 (s); Aug. 2012
- C.H.M. Hofman-Caris, W.G. Siegers; Removal efficiency of pharmaceuticals in drinking water production; Application of affinity adsorption techniques; BTO 2012.010(s); 2012
- C.H.M. Hofman-Caris, B.A. Wols, D.J.H. Harmsen; Removal efficiency of pharmaceuticals in drinking water production; Application of UV/peroxide oxidation; BTO 2012.211(s); 2012
- Sabrina Botton, Emile Cornelissen; Removal efficiency of pharmaceuticals in drinking water production; Application of nanofiltration; BTO 2012.008(s); 2012
- B.A. Wols, D. Vries, C.H.M. Hofman-Caris; Removal efficiency of pharmaceuticals in drinking water production; Application of QSARs; BTO 2012.228 (s) 2012

This report gives an overview of all results obtained in this project, and makes an attempt to integrate the results and compare the different treatment techniques.

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Summary

At the moment over 4000 active ingredients are used as pharmaceuticals. Waste water purification plants in general have not been designed to deal with such compounds, as a result of which many of these compounds and their metabolites can be found in surface water and ground water and possibly end up in drinking water in low concentrations.
For the Rhine delta between the year 2002 and 2008 the load of pharmaceuticals recovered in the Rhine at Lobith could be related to the annual sales in the catchment area, excreted fractions by humans, and removal by waste water treatment. For surface waters the contribution of veterinary pharmaceuticals is considered rather small. However, the extraordinary high consumption of some antibiotics in Dutch veterinary practice might still result in relevant contributions, especially for regional surface waters in rural areas. Additionally, for groundwater the contribution of veterinary pharmaceuticals is probably more relevant than human consumption.

In this research a selection was made of 139 pharmaceuticals and some of their metabolites that are most relevant for studies. Two analytical methods were developed. The first method makes use of the HPLC-Orbitrap MS and additionally, a method was developed for the UPLC by which a broad range of polar pharmaceuticals and transformation products can be determined.

For the human health risk assessment in Dutch surface waters and drinking water 17 common pharmaceuticals and 10 transformation products were monitored in the Dutch waters, including surface waters, pre-treated surface waters, river bank filtrates, two groundwater samples affected by surface water and drinking waters. In these samples, 12 pharmaceuticals and 8 transformation products were observed to be present. Concentrations were generally highest in surface waters, intermediate in treated surface waters and river bank filtrates, and lowest (or not detected) in produced drinking water. The toxicological relevance of the observed pharmaceuticals and transformation products was addressed. For these compounds both a substance specific provisional guideline pGLV value and a group pGLV was derived by assuming an additive mechanism of action within each group. Based on the results obtained, no adverse health effects of the studied compounds are expected in (sources of) drinking water in the Netherlands. However, the presence of transformation products with similar pharmacological activities and concentration levels as their parents illustrates the relevance of monitoring transformation products, and including these in risk assessment.
Veterinary pharmaceuticals, especially antibiotics, are used in huge amounts in the Netherlands. These can enter the soil environment by spreading the manure over agricultural land as fertilizer. No veterinary pharmaceuticals were observed in a selection of groundwater samples from rural areas. Nevertheless, literature illustrates that increased amounts of antibiotic resistance genes can be observed in areas where such pharmaceuticals enter the environment. This may eventually form a threat for human health.

There are various water treatment processes that may be used to convert or remove organic micropollutants like pharmaceuticals and their metabolites from drinking water sources: nanofiltration, (affinity) adsorption techniques and UV/H_2O_2 processes. Their effectiveness for pharmaceuticals was studied and compared within the framework of this project.
For nanofiltration a selection of 30 pharmaceuticals was studied. For most pharmaceuticals NF appeared to be a robust barrier. In general, higher rejection values were observed for negatively charged pharmaceuticals compared to neutral and positively charged solutes. Biofouled membranes show a slightly lower removal efficiency, an effect which is mainly observed with small, positively charged hydrophobic molecules.
The removal efficiency of a UV/H_2O_2 process, based on low pressure (LP) UV lamps was studied with a selection of 36 pharmaceuticals. The efficiency of the UV photolysis process strongly depends on the molecular structure of the compounds involved. However, when photolysis is combined with oxidation by hydroxyl radicals, formed by means of photolysis of H_2O_2 added to the mixture, the majority of compounds appears to be efficiently degraded. Only the conversion of some small, hydrophilic compounds (like metformine and guanylurea) will require a disproportionate amount of energy.

A set of 27 pharmaceuticals was used to study the removal efficiency of affinity adsorption techniques. It was found that affinity adsorption is a very interesting technique to remove specific (categories of) pharmaceuticals. Furthermore, it was observed that competition by other compounds like Natural Organic Material (NOM) plays a less important role in affinity adsorption than in e.g. generic adsorption by means of powdered activated carbon.
It was concluded that in general nanofiltration and the UV/H_2O_2 oxidation process are very robust techniques for pharmaceutical removal, whereas affinity adsorption probably will be more suitable as a polishing step, or for removal of certain types of pharmaceuticals, e.g. in a "concentrated" wastewater.

Economic aspects will have to be taken into account too, in assessing the applicability of a technique. In general, the energy required for membrane filtration processes is in the same order of magnitude as the energy demand of a UV/H_2O_2 process. However, both processes have their own characteristics. Apart from the structure and properties of the micropollutants, aspects like recovery and disposal of the concentrate are important for membrane filtration processes. For UV/H_2O_2 processes lamp choice and water quality are important aspects. Therefore, on forehand it will not be possible to conclude which process will be most suitable in a specific case, as this will largely depend on actual local conditions.

Very often the efficiency of water treatment systems to remove "new" contaminants is unknown. By using QSARs (quantitative structure activity relationships) it is possible to link the existing knowledge of a compound's chemical structure to water treatment process properties. QSARs were developed for nanofiltration as well as for the UV/H_2O_2 process. For the NF process, a good QSAR was found using the so called "data-based" approach. However, this QSAR is only valid for Desal HL membranes. The "knowledge-based" approach could not be followed due to uncertainties in the process model. For the UV/H_2O_2 process, a moderate QSAR model was found for the data-based approach. The knowledge-based approach resulted in a good QSAR for hydroxyl radical rate constants, whereas moderate QSARs were found for other physico-chemical parameters used in the process model (quantum yield and molar absorption). However, the "moderate" QSAR models did not pass the external validation tests. This underlines the importance of external validation. The QSARs developed were able to accurately predict compounds rejection in (virgin) Desal HL membranes as well as compound degradation induced by OH radical reactions alone.

All results have been reported in separate reports. This report gives an overview of all previous results. Besides, it makes an attempt to integrate occurrence data and treatment studies by selecting relevant compounds for treatment studies and compare the efficiency of the different treatment processes for the selection of pharmaceuticals.

Contents

1 Introduction

At the moment thousands of active ingredients are used as pharmaceuticals [Beausse, 2004]. Previous research [ter Laak et al., 2010] showed that the observed annual loads for 20 most frequently observed pharmaceuticals in the Rhine at Lobith were similar to the loads predicted from annual sales in the catchment area, excreted fractions by humans and removal by waste water treatment. Waste water purification plants in general have not been designed to deal with such compounds, as a result of which many of these compounds and their metabolites can be found frequently in surface water (up to µg/L) occasionally in ground water and possibly even may end up in drinking water in low concentrations. Besides, veterinary pharmaceuticals may directly enter the environment, as manure/slurry is collected and often used as fertilizer on land.
Although numerous studies have been carried out describing the presence of pharmaceuticals in the water cycle, their transformation products usually were not included. In this study it was shown that the presence of these transformation products, that can have similar pharmacological activities and concentration levels as their parents, cannot be neglected, and have to be included in monitoring and risk assessments.

For the present research project, 139 compounds were selected by identifying the most relevant pharmaceuticals and metabolites for the water cycle in the Netherlands, based on occurrence, human and veterinary consumption (sales data), excretion, metabolism and (if available) persistence in the environment. A method was developed covering 50 pharmaceuticals and 18 transformation products based on analytical possibilities and physico-chemical properties. These pharmaceuticals were studied in drinking water sources. Subsequently, three different sub-sets of pharmaceuticals were selected and applied to study the removal efficiency of three different technologies (UV/H_2O_2 processes, nanofiltration, and (affinity) adsorption. One of the goals of this research was to find a way to compare the efficiency of these different techniques. Furthermore, it would be a great help if it would be possible for new, unknown compounds, to predict which technique will be most efficient for removal. For these purposes, it was tried to develop "Quantitative Structure-Activity Relationships" (QSARs). QSARs are based on a statistical relation between some structural features of the molecule and its behavior. In order to develop such QSARs a large amount of experimental data is required, which was obtained by testing the three techniques. Furthermore, an attempt was made to compare the different processes based on other aspects, like energy demand.

2 Selection of pharmaceuticals

2.1 Pharmaceuticals relevant for the water cycle

Over 4000 active ingredients are used as pharmaceuticals [Beausse, 2004]. The presence of these pharmaceuticals in surface water, groundwater and drinking water depends on numerous factors: consumption, metabolism by the user (human and live stock), removal in the waste water treatment (human) or storage tanks of slurry (live stock), sorption and biodegradation in the environment (in surface water, sediment, groundwater and soil), hydrology of acquifers, and treatment steps in drinking water production plants. Based on consumption data [Miege et al., 2008; Oosterhuis et al., 2011; Rohweder, 2003; van der Aa et al., 2011] and occurrence in the environment [Monteiro and Boxall, 2010] a list of over 400 pharmaceuticals was composed. From this list a primary selection of 139 compounds was made by identifying the most relevant pharmaceuticals and metabolites for the water cycle based on occurrence, human and veterinary consumption, excretion, metabolism and (if available) persistence in the environment. This selection is shown in Table 2-1. More information can be found in BTO report BTO 2011.100 (s).

Table 2-1: Relevant pharmaceuticals in the water cycle

Pharmaceutical [1]	Class	human or veterinary use	Consumption [2]	Log Kow [3]	Occurrence SW [4]	Occurrence GW [4] (references)	Occurrence DW [4] (references)
17-alpha-ethinylestradiol	Endocrine disruptor	H	low	3.67	k	k	
Acetyl salicylic acid	Analgetic	H	14294	1.19	b, a, k		
Acetyl salycilic acid metabolite: Salicylic acid (also used as disinfectant)	Analgetic	H		2.26	c, k	c	c
Allopurinol	Analgesic	H	3987, high	-1.14			
Aminophenazone (aminopyrine)	Analgesic	H	low	1.0	a		
Aminophenazone metabolite: Dimethylaminophenazone	Analgesic	H		polar	k		
Amoxicillin	Antibiotic	H/V	20263, 1187 (V), high	0.87	a, k		
Atenolol	Cardiovascular	H	4018 med	0.16	b, d, a, e, k		
Bezafibrate	Lipid Regulator	H	med	4.25	b, a, e, c, k	c	c
Bisoprolol	Cardiovascular	H	low		d, a, k		
Caffeine	Stimulant	H		-0.07	b, k	g, k	
Carbamazepine	Neurologic	H	8400, high	2.45	b, f, a, e, c, k	i, c, k	c
Carbamazepine matebolite: 10,11-Dihydro-10-hydroxy carbamazepine	Neurologic	H		0.93			
Carbamazepine matebolite: 10,11-trans diol Carbamazepine (20%)	Neurologic	H		polar			
Carbamazepine matebolite: Carbamazepine 10,11-epoxide	Neurologic	H		0.95		i	
Chloramphenicol	Antibiotic	H	low		b, e, k		
Chlorotetracycline	Antibiotic	V					
Cimetidine	H2 Receptor Antagonist	H	med	0.4			
Ciprofloxacin	Antibiotic	H	2387, med	0.28			

Clarithromycin	Antibiotic	H	2399, med	3.16	b, a, k	j	
Clenbuterol	Bronchodilator	H	low	2.0			
Clindamycin	Antibiotic	H	med	2.16	b, a, e		
Clofibrate metabolite: Clofibric acid	Lipid Regulator	H		2.57	b, a, e, k	i, c	c
Cortisol	Endocrine disruptor	H		1.61			
Cortisol glucuronide	Endocrine disruptor	H					
Cortisol sulfate	Endocrine disruptor	H					
Cortisone	Endocrine disruptor	H		1.47			
Cyclophosphamide	Anticarcinogen	H		0.63	e, k		
Diatrizoic acid = Amidotrizoic acid	X-ray contrast liquid	H	high	1.37	b, a		
Diclofenac	Analgetic	H	6227, high	4.51	b, d, a, e, c, k	c, k	
Diclofenac matebolite: 4'-hydroxy diclofenac	Analgetic	H		3.7			
Diclofenac metabolite: (3 ,4' , 5' en 4'-5)hydroxy diclofenac (65%)	Analgetic	H		nvt			
Diclofenac metabolite: 3'-hydroxy 4'-methoxy diclofenac	Analgetic	H		3.01			
Diclofenac metabolite: 3-hydroxy diclofenac	Analgetic	H		3.7			
Diclofenac metabolite: 4'-5-dihydroxy diclofenac	Analgetic	H		2.35			
Diclofenac metabolite: 5'-hydroxy diclofenac	Analgetic	H		3.7			
Dimetridazole	Analgetic	V			a		
Doxycycline	Antibiotic	H/V	190906(V), med		k		
Enalapril	Cardiovascular	H	med	2.45	f, d, k		
Enalaprilat	Cardiovascular	H	med	-0.74	k		
Erythromycin A / Erythromycin h2o	Antibiotic	H/V	med	3.06	b, a, k	k	
Erythromycine metabolite: Anhydro erythromycin A	Antibiotic	H/V	med	3.06	b, a		
Fenoprofen	Analgetic	H		3.9	b, a, k		
Fluoxetine (prozac)	Neurologic	H		4.05	d, e, c, k	g, c	c
Fluoxetine metabolite: Norfluoxetine	Neurologic	H		4.2	k		
Flurazepam	Neurologic	H		3.02			
Flurazepam metabolite: Desalkyl flurazepam	Neurologic	H		2.32	f		
Gemfibrozil	Neurologic	H	5148, med	4.77	b, a	g	
Gemfibrozil metabolite: Carboxy gemfibrozil	Neurologic	H					
Gemfibrozil metabolite: Gemfibrozil 1-O-glucuronide	Neurologic	H		2.14			
Hydrochlorothiazide	Cardiovascular	H	5316, high	-0.07	k		
Ibuprofen	Analgetic	H	28884, high	3.97	b, a, e, k	g, c	c
Ibuprofen metaboliet: hydroxy ibuprofen	Analgetic	H		2.29	k		

Ibuprofen metabolite: Ibuprofen Acyl-ß-D-glucuronide	Analgetic	H					
Ifosfamide	Anticarcinogen	H	low	0.86	e, k		
Iopamidol	X-ray contrast liquid	H	med	-2.42	b, a, c, k	k	
Iopromide	X-ray contrast liquid	H	high	-2.05	b, a, c, k	h, k	c
Irbesartan	Cardiovascular	H	12388, med	5.31			
Isosorbide mononitrate	Cardiovascular	H	2483, med	-0.4			
Ivermectin (dihydroavermectin)	Antiparasitic	V		4.48			
Ketoprofen	Analgetic	H	low	3.1	b, a, k		
Levetiracetam	Neurologic	H	4764	-0.49			
Lidocaine	Cardiovascular	H		2.44	b, d, a, e		
Lincomycin	Antibiotic	H/V	424.9 (V)	0.2	a, e, k	g	
Loratidine	Anti-histamine	H		relatively hyrofobic			
Losartan	Cardiovascular	H	5628, med	4.01	f, d		
Mebendazole	Antiparasitic	V			a		
Metamizole	Analgetic	H	high	-4.76			
Metamizole metabolite: N-acetyl-4-aminoantypyrine	Analgetic	H			k		
Metamizole metabolite: N-formyl-4-aminoantypyrine	Analgetic	H			k		
Metformin	Antidiabetic	H	207190, high	-2.64	k		
Metoprolol	Cardiovascular	H	22681, high	1.88	b, a, e, c, k		c
Metoprolol metabolite: 4-(2hydroxy-3-isopropylamino-proproxy)phenylacetic acid (65%)	Cardiovascular	H					
Metoprolol metabolite: Alpha-hydroxy metoprolol (10%)	Cardiovascular	H		0.56			
Metoprolol metabolite: Metoprolol-glucuronide	Cardiovascular	H		-0.12			
Metoprolol metabolite: O-desmethyl metoprolol	Cardiovascular	H		1.28			
Metronidazole	Antibiotic	H	med		b		
Naproxen	Analgetic	H	11472, med	3.18	b, d, a, e, k		
Naproxen metabolite: (R)-O-Desmethyl Naproxen	Analgetic	H		2.82			
Niacin (vitamine B3, nicotinezuur)	Vitamin	H	0.4				
Omeprazole	H2 Receptor Antagonist	H	med		k		
Omeprazole metabolite: 5-hydroxyomeprazole	H2 Receptor Antagonist	H					
Omeprazole metabolite: Esomeprazole	H2 Receptor Antagonist	H	high				

Omeprazole metabolite: omeprazole sulfone	H2 Receptor Antagonist	H					
Oxazepam	Neurologic	H	low	2.24	f, d, e		
Oxytetracycline	Antibiotic	H/V	Low, 299298 (V)	-1.72	a, k		
Oxytetracycline metabolite: 4-epi-ocytetracycline	Antibiotic	H/V		-0.91			
Oxytetracycline metabolite: Beta-apo oxytetracycline	Antibiotic	H/V		-0.16			
Pantoprazol	H2 Receptor Antagonist	H	3190, low				
Paracetamol (Acetaminophen)	Analgetic	H	104714, high	0.46	d, a, c, k	g, c	c
Paracetamol metabolite: 4-Acetamidophenyl-ß-D-Glucuronide	Analgetic	H					
Paracetamol metabolite: 4-Acetaminophen Sulfate	Analgetic	H					
Paroxetine	Neurologic	H	low	3.95			
Penicillin V = Phenoxymethylpenicillin	Antibiotic	H/V	96063 (V), high	2.09	k		
Pentoxifylline	Cardiovascular	H	high	0.29	b, a, e, k		
Phenazone	Analgesic	H	med	0.38	b, d, a, c, k	i, c, k	c
Phenazone metabolite: 1-acetyl-1-methyl-2-fenylhydrazide (AMPH)	Analgesic	H				i	
Phenazone metabolite: N-formyl aminoantipyrine	Analgesic	H					
Pindolol	Cardiovascular	H	low	2.0			
Prednisolone	Endocrine disruptor	H/V	low	1.62			
Prednisolone metabolite: 6-alpha methyl prednisolone	Endocrine disruptor	H		1.62			
Propranolol	Cardiovascular	H	med	3.5	d, a, k		
Propyphenazone	Analgesic	H	med	1.94	b, e, k	k	
Ranitidine	H2 Receptor Antagonist	H	7044, high	0.27	k		
Salbutamol	Bronchodilator	H	low	0.64	k		
Sildenafil (viagra)	Vascular	H		2.3			
Sotalol	Cardiovascular	H	3992, med	0.24	b, a, e, k	k	
Sulfachloropyridazine = Sulfaclozine	Antibiotic	H/V		0.31			
Sulfachloropyridazine metabolite: N4-acetyl Sulfachloropyridazine	Antibiotic	H/V					
Sulfadiazine	Antibiotic	V		-0.09	a, e	k	
Sulfadiazine metabolite: Acetyl sulfadiazine	Antibiotic	V		0.39			
Sulfadimidine (Sulfametazine)	Antibiotic	H					
Sulfamethoxazole	Antibiotic	H/V	3165, high	0.89	b, a, e, c, k	g, h, c, k	c
Sulfamethoxazole metabolite: N4-acetyl Sulfamethoxazole	Antibiotic	H/V		1.21	k		

Sulfaquinoxalin	Antibiotic	V		1.68			
Sulfaquinoxalin metabolite: N4-acetyl Sulfaquinoxalin	Antibiotic	V		2.23			
Sulfasalazine	Analgetic	H		3.81			
Sulfasalazine metabolite: Mesalazine	Analgetic	H		0.98			
Temazepam	Neurologic	H	med	2.19	f, d		
Terbutaline	Bronchodilator	H	low	0.9	a, k		
Tetracycline	Antibiotic	H/V	low	-1.3	k	k	
Theophylline	Bronchodilator	H	high				
Tramadol	Analgetic	H	3516, med	3.01	e		
Tramadol metabolite: N-Desmethyltramadol	Analgetic	H					
Tramadol metabolite: O-Desmethyltramadol	Analgetic	H					
Trimethoprim	Antibiotic	H/V		0.91	a, e, k		
Trimethoprim metabolite: dihydroxy trimethoprim	Antibiotic	H/V					
Trimethoprim metabolite: hydroxy trimethoprim	Antibiotic	H/V					
Trimethoprim metabolite: Pyrimidine iminoquinone methide	Antibiotic	H/V					
Tylosin / Tilmicosin	Antibiotic	V		1.63	a		
Valsartan	Cardiovascular	H	6123, high	3.65	b, f		
Valsartan metabolite: 4-hydroxy valsartan	Cardiovascular	H					
Venflaxatine metabolite: O-desmethylvenlafaxine	Neurologic	H					
Venlafaxine	Neurologic	H	3100	3.28			
Venlafaxine metabolite: D,L N-desmethyl venlafaxine	Neurologic	H					
Venlafaxine metabolite: D,L-N,N-didesmethyl venlafaxine	Neurologic	H					
Venlafaxine metabolite: Dehydro venlafaxine	Neurologic	H					
Venlafaxine metabolite: O-desmethyl-(rac-venlafaxine)Glucuronide	Neurologic	H					
Verapamil	Cardiovascular	H	3187, high	3.79			
Verapamil metabolite: Norverapamil	Cardiovascular	H					

2.2 Selection of pharmaceuticals for screening of human health risks

Several studies are available on the human health risk of exposure to low concentrations of pharmaceuticals in (sources of) drinking water. However, not much is known yet on the risk of exposure to transformation products of pharmaceuticals through (drinking) water. In an attempt to address this question, a human health risk assessment was performed on a selection of pharmaceuticals and metabolites that were observed in the screening study covering surface water, river bank filtrate and drinking water derived from these sources. This selection is shown in Table 2-2.

Table 2-2: List of pharmaceuticals and metabolites selected for screening of human health risks and their occurrence in various surface water-related waters.

	Surface water	Raw intake water	Drinking water
Phenazone	X	X	X
Propyphenazone		X	
AMPH *	X	X	X
AAA and FAA *	X	X	
Tramadol	X	X	
Sulfamethoxazole	X	X	
Erythromycin-H_2O	X	X	
Clindamycin	X		
Carbamazepine	X	X	
Carbamazepine-10,11-epoxide *	X		
Metoprolol	X	X	
Sotalol	X	X	
Atenolol	X		
Venlafaxine	X	X	
O-desmethyl-venlafaxine *	X		
Bezafibrate	X		

* Transformation products

N.B. This selection was made based on analyses using the conventional analytical method. This method appeared not to be suitable for analysis of all occurring pharmaceuticals, as a result of which compounds like metformine, which often is present in a relatively high concentration, were not detected. Within the framework of this project new analytical techniques were developed (see section 2.5), which can be applied to a broader range of pharmaceuticals. This new range for example also includes metformine and its transformation product guanylurea, and hydroxyibuprofen.

2.3 Selection of compounds for the study of the efficiency of treatment processes

Subsequently, pharmaceuticals were selected for research with three different treatment techniques, taking into account the requirements for the development of QSARs. A literature study was carried out on the removal of the compounds in Table 2-1 by water treatment processes (nanofiltration (NF), reverse osmosis (RO), oxidation processes, adsorption to activated carbon, waste water treatment, and processes like river bank filtration). For each treatment technique in this study, a selection of relevant pharmaceuticals was made. An overview of all compounds selected for this purpose and their chemical structure is shown in Appendix I (table I-1).

2.3.1 Set of pharmaceuticals for nanofiltration

For the effectiveness of nanofiltration, the size of the compound is the most important parameter. Usually the molecular weight cut off (MWCO) of the membrane is used to indicate the lower limit of molecules that cannot pass the membranes' pores. The hydrophobicity and charge of a compound can change the apparent size of the compounds as seen by the membrane. As these changes are rather small, they are only relevant when the size of the compound is close to the size of the pores in the membrane. The hydrophobicity of neutral membranes is indicated by log K_{ow}, in which K_{ow} is the distribution coefficient of the compound in an organic solvent and water. For charged molecules log D is used, D being the distribution coefficient of the sum of all forms of the compound (ionized and non-ionized) in an organic solvent and water. For the selection molecules from Table 2-1 were chosen with a molecular weight < 1.5*MWCO, with known physicochemical data (log K_{OW}, log D, pKa). For charged compounds, pharmaceuticals from the following categories were chosen:

- Log D_{pH7} < 0 (hydrophilic)
- 0 < Log D_{pH7} < 2
- Log D_{pH7} > 2 (hydrophobic)

Furthermore, it was made sure that the selection contained molecules that were negatively or positively charged, or neutral at pH = 7
Besides, a cross section was made with compounds selected for either UV/H_2O_2 processes or (affinity) adsorption studies. The selection is shown in table I-2.

2.3.2 Set of pharmaceuticals for UV/H_2O_2 processes

For a UV/H_2O_2 advanced oxidation process, conversion of the target molecules depends on both photolysis and oxidation by hydroxyl radicals. Within the selection of Table 2-1 those compounds were chosen, which, according to literature data, are sensitive only to photolysis, only to oxidation, to both photolysis and oxidation, or neither to photolysis nor oxidation. From the large amount of compounds in Table 2-1 for which the sensitivity was unknown, the compounds selected previously for NF were taken. Besides, glucocorticoids, like cortisone, cortisol and prednisolone were selected, resulting in a total of 36 compounds, shown in table I-3.

2.3.3 Sets of pharmaceuticals for adsorption processes

For adsorption of a compound the size of the molecule and its interaction with the surface of the sorbent are of primary importance. If a solution containing a mixture of small and large molecules is used, in general first the small molecules will be adsorbed (because of their faster diffusion to the surface). However, later these may be replaced by larger molecules, which, due to the fact that they have more points for interaction with the surface, are adsorbed irreversibly. For the interaction with the surface, log D may also be of importance, depending on the type of surface interactions involved. Log D is the logarithm of the ratio of the sum of the concentrations of all forms of the compound (ionized plus non-ionized) in each of the two phases (usually octanol and water) at a certain pH.
Furthermore, the presence of functional groups that may show a specific interaction with the adsorbent surface can play an important role. This is especially the case for affinity adsorption, which is based on the principle of specific interactions between the adsorbent surface and functional groups. For this part of the project, compounds from the following categories were selected:

- Log D_{pH7} < 0 (hydrophilic)
- 0 < Log D_{pH7} < 2
- Log $D_{pH}7$ > 2 (hydrophobic)

Furthermore, it was made sure that the selection contained compounds that were negatively or positively charged, or neutral at pH = 7, and that they covered a wide range of molecular weights. Besides, an overlap with the selections for UV/H_2O_2 processes and nanofiltration was used, making sure that all compounds at least contained one of the following functional groups: an acid (COOH), a

hydroxyl group (OH), a base (NH or NH_2), or a phenyl group. The final selection is shown in tables I-4 and I-5.

An overview of all selected compounds, for nanofiltration, UV/H_2O_2 as well as adsorption, is given in Table 2-3.

Table 2-3: overview of selected compounds for further research

compound	NF	UV/H_2O_2	adsorption
4-(2-hydroxy-3-isopropylamino-propoxy) phenylacetic acid			X
Acetyl salicylic acid			X
Aminophenazone (aminopyrine)	X	X	X
Amoxilline			X
Atenolol	X	X	X
Bezafibrate	X	X	X
Carbamazepine	X	X	X
ciprofloxacin	X	X	X
Clenbuterol	X	X	
Clofibrate metabolite: clofibric acid	X	X	X
Cortisol		X	X
Cortisone		X	X
Cyclophosphamide	X	X	X
Diatrizoic acid		X	X
Diclofenac	X	X	X
Doxycycline		X	X
Erythromycin			X
Fenoprofen	X	X	
Fluoxetine metabolite: norfluoxetine	X	X	
Gemfibrozil	X	X	X
Hydroxyl ibuprofen			X
Ibuprofen	X	X	X
Ketoprofen	X	X	
Metamizole			X
Metformin	X	X	X
Metoprolol	X	X	X
Metronidazole		X	
Naproxen	X	X	X
Niacin	X	X	
O-desmethyl-metoprolol			X
Oxazepam			X
Paracetamol (acetaminophen)	X	X	X
Paroxetine	X	X	X
Pentoxifylline	X	X	X
Phenazone	X	X	X
Pindolol	X	X	X
Prednisolone		X	X
Propyphenazone			X
Propranolol	X	X	
Salbutamol	X	X	X
Salicylic acid			X
Sotalol	X	X	X
Sulfadiazine	X	X	X
Sulfamethoxazole	X	X	X
Temazepam			X
Terbutaline	X	X	
Trimethoprim	X	X	X
Verapamil			X

2.4 Quantitative Structure-Activity Relationships (QSARs)

Quantitative Structure-Activity Relationships (QSARs) and Quantitative Structure-Property Relationships (QSPRs) may be used to predict the removal efficiency for various techniques. By combining experimental data, descriptors were defined for nanofiltration and for the UV/H_2O_2 process. Data were obtained form the experimental work carried out in this project and from literature. The molecular structures involved are shown in table I-1.

2.5 Analytical methods

Two analytical methods were developed, by means of which aqueous solutions of these pharmaceuticals can be analyzed: reversed phase UHPLC and normal phase HILIC [LOA-548 and LOA-602; Kooij, 2008 and 2012]. Details on the repeatability, detection limit and reporting limit are shown in table II-1.

2.6 More information

A complete overview of the selections of pharmaceuticals for several purposes, made in this project, and details on the analytical methods applied can be found in

- Kooij P., HPLC-Orbitrap MS analyse van geneesmiddelen in drink-, grond- en oppervlaktewater; KWR-huisvoorschrift LOA 602, Nieuwegein, The Netherlands (2008)
- Kooij P., Bepaling van geneesmiddelen en metabolieten in water met behulp UPLC-MS/MS. KWR, KWR-huisvoorschrift LOA 548, Nieuwegein, The Netherlands (2012).
- Thomas ter Laak, Bas Hofs, Cindy de Jongh, Bas Wols, Roberta Hofman-Caris; Selecting relevant pharmaceuticals and metabolites for monitoring, risk assessment and removal efficiency studies; BTO 2011.100 (s), July 2011
- Appendix I and II.

3 Pharmaceuticals (and their transformation products) in Dutch waters

3.1 A mass balance approach for the river Rhine

At nine sampling locations in the Rhine delta 48 to 127 pharmaceuticals, X-ray contrast media and endocrine disrupting chemicals were frequently monitored between the year 2002 and 2008. Data were obtained from RIWA Rijn. Both spatial variation in concentrations of pharmaceuticals and temporal variation at the Dutch sampling locations Lobith and Nieuwegein were studied. The sampling locations are shown in Figure 3-1.

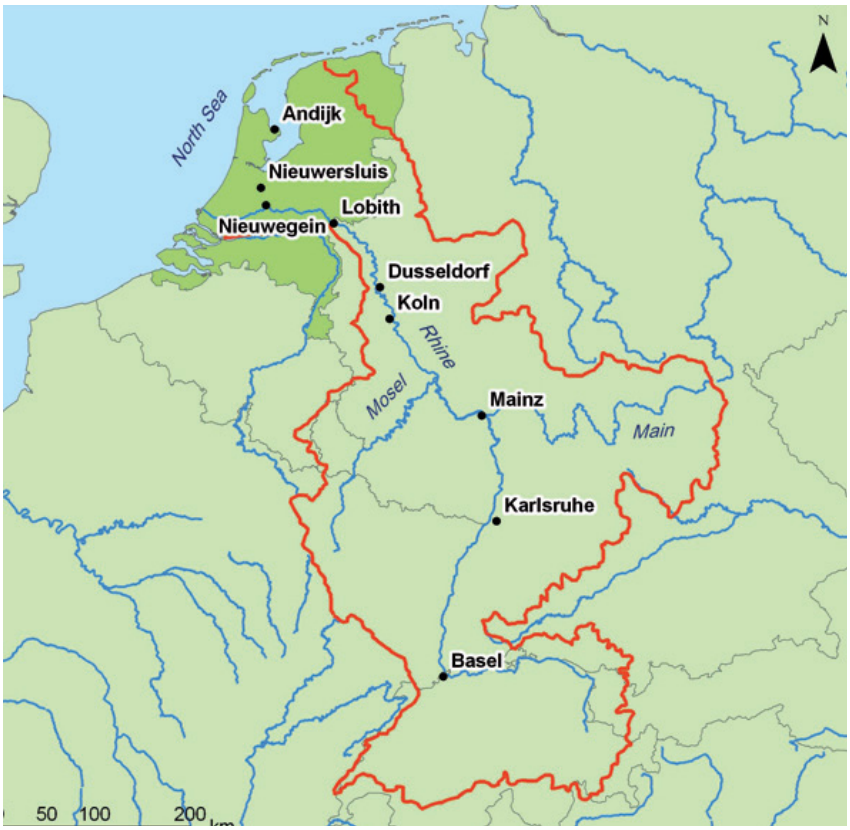

Figure 3-1: The sampling locations along the Rhine, the red line is the border of the Rhine catchment area. The distances of the sampling locations from the Bodensee are: Basel = 164 km, Karlsruhe = 359 km, Mains = 501 km, Köln = 686 km, Düsseldorf = 722 km, Lobith = 860 km, Nieuwegein = 950 km.

Average concentrations of several X-ray contrast mediums were shown to be above 0.1 µg/L, the average concentration of carbamazepine was about 0.1 µg/L, while average concentrations of the other pharmaceuticals generally fell between 0.01 and 0. 1 µg/L. These concentrations were used to calculate the annual loads transported by the Rhine at Lobith. It was found that some pharmaceuticals (like e.g. diclofenac, ibuprofen and bezafibrate) showed clear seasonal trends: high loads entering the Netherlands in winter and up to ten times lower loads in summer. These trends can be a result of increased

degradation in the wastewater treatment (and river) as a result of higher temperatures or variations in consumption.
The loads were compared to loads predicted from annual sales in the catchment area, excreted fractions by humans and removal by waste water treatment. It was observed that, on average, 25% of the pharmaceuticals consumed by the inhabitants of the Rhine catchment could be recovered in the Rhine. Despite incomplete consumption data, no correction for medication compliance or degradation and sorption in the environment, the actual recovered fractions deviated less than a factor two from predicted fractions for 15 out of 20 pharmaceuticals. For five pharmaceuticals the actual recovered concentrations in the Rhine were lower than expected. This can be explained by sorption and degradation processes in the environment that were not included in the prediction of environmental residues.
The translation from predicted loads to concentration appeared not to be straightforward. Frequent sampling in this study illustrated that concentrations in the Rhine can vary by more than an order of magnitude, and that this variation is not completely explained by variations in fluxes of water in the Rhine (i.e. dilution). Consequently, frequent monitoring remains necessary in order to provide information on temporal fluctuations of concentrations.

3.2 Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water

3.2.1 Screening of pharmaceuticals and their transformation products

Many studies describe the presence of pharmaceuticals in the water cycle, however, their transformation products usually are not included. In this study a selection of 17 common pharmaceuticals and 10 transformation products was monitored in the Dutch waters, including surface waters, pre-treated surface waters, river bank filtrates, two groundwater samples affected by surface water, and the produced drinking waters. In these samples, 12 pharmaceuticals and 8 transformation products were observed to be present. Concentrations were generally highest in surface waters, intermediate in treated surface waters and river bank filtrates, and lowest or not detected in produced drinking water. The lower (or even undetectable) concentrations in river bank filtrates can be explained by degradation and soil sorption during infiltration. However, only for phenazone and its environmental transformation product AMPH significantly higher concentrations were found in river bank filtrates. This was likely due to historical contamination that is still present in river bank filtrates, as these filtrates in general consist of mixtures of younger (months to years) and older (decades or even longer) water.
Transformation products of some pharmaceuticals were observed in similar concentrations as their parents. Fairly constant ratios were observed between concentrations of transformation products and parent pharmaceuticals. This might enable prediction of concentrations of transformation products from concentrations of parent pharmaceuticals.

Table 3-1: Average concentrations of observed pharmaceuticals (ng/L) in surface waters (SW), in pre-treated waters originating from surface waters (pre-treated SW), in drinking water obtained from surface water (DW-SW), in river bank filtrates (RBF) land in drinking water obtained from river bank filtrates (DW-RBF). Maximum concentrations and number of positive samples per compounds are given between brackets. Pharmaceuticals and transformation products from the same pharmacological class are grouped.

Compound	SW (n=14)	Pre-treated SW (n=10)	DW-SW (n=10)	RBF (n=5)	DW-RBF (n=5)
Phenazone	9 (25, 6)	6 (21, 3)	- [2]	135 (258, 5)	20 (35, 3)
dimethylaminophenazone	- [2]	- [2]	- [2]	15 (22, 5)	- [2]
Propyphenazone	- [2]	- [2]	- [2]	12 (20, 4)	- [2]
1-acetyl-1-methyl-2-phenylhydrazide (AMPH) [1]	16 (66, 8)	7 (19, 5)	- [2]	109 (172, 5)	10 (19, 3)
4-acetylaminoantipyrine (AAA) [1]	76 (176, 10)	28 (124, 4)	- [2]	(20) [3]	- [2]
4-formylaminoantipyrine (FAA) [1]	49 (164, 7)	23 (147, 2)	- [2]	(45) [3]	- [2]
Tramadol	51 (107, 12)	19 (53, 7)	- [2]	- [2]	- [2]
O-desmethyltramadol [1]	17 (78, 8)	- [2]	- [2]	- [2]	- [2]
erythromycin-H20 [1]	10 (35, 4)	(17) [3]	- [2]	- [2]	- [2]
clindamycine	5 (16, 2)	- [2]	- [2]	- [2]	- [2]
carbamazepine	59 (121, 12)	29 (50, 8)	- [2]	27 (48, 5)	- [2]
carbamazepine 10,11-epoxide [1]	17 (35, 11)	6 (14, 6)	- [2]	- [2]	- [2]
hydroxycarbamazepine [1,4]	17 (35, 14)	8 (15, 9)	- [2]	7 (11, 5)	1 (3, 3)
oxcarbazepine	(8) [3]	- [2]	- [2]	- [2]	- [2]
atenolol	6 (26, 6)	- [2]	- [2]	- [2]	- [2]
metoprolol	41 (107, 12)	5 (16, 3)	- [2]	- [2]	- [2]
sotalol	31 (99, 9)	- [2]	- [2]	- [2]	- [2]
venlafaxine	21 (59, 11)	5 (13, 3)	- [2]	- [2]	- [2]
O-desmethylvenlafaxine [1]	32 (112, 7)	- [2]	- [2]	- [2]	- [2]
bezafibrate	5 (17, 2)	- [2]	- [2]	- [2]	- [2]

[1] Transformation product; [2] Compound could not be quantified in the sample
[3] If a compound is only observed in one sample, the observed concentration is listed between brackets
[4] No standard of hydroxycarbamazepine was injected so identification is not verified and concentrations are calculated assuming an equal response of carbamazepine and hydroxycarbamazepine

It seems that there is no statistical difference between surface water and pre treated surface water, but this does not mean that there is no effect of the water pre-treatment. As both the composition of the influent water and the pre-treatment of surface waters is very diverse, no simple conclusions can be drawn.

For some compounds, like e.g. tramadol, velofaxine and carbamazepine, it was shown that the wastewater treatment process is approximately equally effective in removing the parent and transformation product. For other compounds this remains to be studied.

3.2.2 Toxicological relevance of pharmaceuticals and transformation products

Most human health risk assessments of pharmaceuticals and other anthropogenic compounds in drinking water assess the risks of exposure to individual compounds and do not address mixture toxicity. In this study a quantitative consideration for mixture toxicity was taken into account, by deriving so-called group pGLVs for groups of pharmaceuticals with a shared pharmacological mechanism of action. Additive effects of the compounds within each group were assumed. The phenazone-type drugs include transformation products based on a common analgesic effect, the carbamazepine-type drugs include oxcarbazepine and transformation products based on a common pharmacological mechanism of action, and the group of beta-blockers consists of compounds with a common β-receptor antagonistic activity. The other parent compounds in this study shared no common mechanism of action. For the remaining compounds groups consisting of a parent compound and its corresponding transformation product were formed, under the assumption of an equivalent pharmacological or toxicological potency. After this classification, a group pGLV for each group was

derived. This group pGLV was set at the level of the lowest pGLV within the group as a conservative approach. For each group the maximum (sum) concentration levels present in the different water samples were divided by the (group) pGLVs. For the compounds and the compiled groups in this study, all quotients were below 1 and also below the thresholds to carry out an additional assessment of 0.2 and 0.1 for sources of drinking water and drinking water, respectively. These findings imply that the compounds observed in the water samples present no appreciable concern to human health. The data and parameters used for the derivation of the pGLVs for the pharmaceuticals and transformation products detected is shown in *Table 3-2*.

Table 3-2: A) Data and parameters used for the derivation of provisional drinking water guideline values (pGLV) and (group) pGLVs for each (group of) pharmaceuticals and B) Comparison of the maximum (sum) concentration levels present in the different water samples (see Table 1) to the pGLV expressed as quotients.

Compound	Point of departure	Ref	UF	TDI or ADI (mg/kg bw/d)	pGLV (µg/L)	Group pGLV (µg/L)	Quotient DW-RBF	Quotient pre-treated SW	Quotient RBF	Quotient SW
phenazone	lowest daily therapeutic dose of 3.6 mg/kg bw/day for phenazone	1,2	100	0.036	125	35	0.002	0.009	0.02	0.01
dimethylaminophenazone	pharmacological NOEL of 10 mg/kg bw/d for metamizole	3	1000	0.010	35					
propyphenazone	lowest daily therapeutic dose of 2.1 mg/kg bw/day for propyphenazone	4	100	0.021	75					
1-acetyl-1-methyl-2-phenylhydrazide (AMPH)	pharmacological NOEL of 10 mg/kg bw/d for metamizole	3	1000	0.010	35					
4-acetylaminoantipyrine (AAA)	pharmacological NOEL of 10 mg/kg bw/d for metamizole	3	1000	0.010	35					
4-formylaminoantipyrine (FAA)	pharmacological NOEL of 10 mg/kg bw/d for metamizole	3	1000	0.010	35					
tramadol	lowest daily therapeutic dose of 0.71 mg/kg bw/d for tramadol	4	100	0.0071	25	6	-	0.009	-	0.03
O-desmethyl-tramadol	lowest daily therapeutic dose of 0.71 mg/kg bw/d for tramadol	4	400	0.0018	6					
erythromycin-H20	microbiological ADI of 4.3 µg/kg bw/day for erythromycin	1,2	na	0.0043	15	na	-	0.001	-	0.002
clindamycine	microbiological NOEL of 3 mg/kg bw/d for clindamycin	5	100	0.030	105	na	-	-	-	0.0002
carbamazepine	lowest daily therapeutic dose and lowest LOAEL of 1.43 mg/kg bw/d for carbamazepine	6	90	0.016	56	56	0.00005	0.001	0.001	0.004
carbamazepine-10,11-epoxide	lowest daily therapeutic dose and lowest LOAEL of 1.43 mg/kg bw/d for carbamazepine	6	90	0.016	56					
hydroxycarbamazepine	lowest daily therapeutic dose and lowest LOAEL of 1.43 mg/kg bw/d for carbamazepine	6	90	0.016	56					
oxcarbazepine	lowest daily therapeutic dose of 8.6 mg/kg bw/d for oxcarbazepine	4	100	0.086	300					
atenolol	lowest daily therapeutic dose of 0.71 mg/kg bw/d for atenolol	4	100	0.0071	25	25	-	0.0006	-	0.009
metoprolol	lowest daily therapeutic dose of 1.4 mg/kg bw/d for metoprolol	2,7	100	0.014	50					
sotalol	lowest daily therapeutic dose of 1.1 mg/kg bw/d for sotalol	4	100	0.011	40					
venlafaxine	lowest daily therapeutic dose of 0.54 mg/kg bw/d for venlafaxine	4	100	0.0054	19	19	-	0.0007	-	0.01
O-desmethylvenlafaxine	lowest daily therapeutic dose of 0.71 mg/kg bw/d for O-desmethylvenlafaxine	4	100	0.0071	25					
bezafibrate	lowest daily therapeutic dose of 1 mg/kg bw/d for bezafibrate	1	100	0.010	35	na	-	-	-	0.0005

UF, uncertainty factor; ref, references; TDI, Tolerable Daily Intake; ADI, Acceptable Daily Intake; pGLV, provisional guideline value; DW-RBF, drinking water produced from river bank filtrate; SW, surface water; RBF, river bank filtrate. References: 1 (Versteegh et al., 2007), 2 (Schriks et al., 2010), 3 (EMEA, 2003), 4 (Medicines Complete, 2011), 5 (WHO, 2000), 6 (Cunningham et al., 2010), 7 (Versteegh et al., 2003)

This study illustrates that, when taking into account potential additive effects, current environmental concentrations and concentrations in drinking water of pharmaceuticals and their transformation products are well below levels where potential effects on human health would be expected. However, alertness may be required as presence of these compounds in (sources) of drinking water may change in future. More thorough monitoring yielding information on statistical uncertainty and variability in time and space may be recommended as concentrations of pharmaceuticals can vary in time. Additionally, a potential drawback of this practical approach is that only additive effects within a group are taken into account. Synergistic effects of mixtures of compounds within a pharmacological class are largely unknown. In the report "Humane Geneesmiddelen in de waterketen; kennismontage" that is currently written, summarizes all available knowledge on the occurrence and effects of human pharmaceuticals in the water cycle, and the possibilities to reduce their concentration (Derksen and Ter Laak, in prep.).

3.3 Pharmaceuticals in the Province of Limburg

The study "Geneesmiddelen in de Watercyclus in Limburg" discussed the origin, distribution and effects of pharmaceuticals and transformation products for the environment and the raw water quality of drinking water production location Heel. The study was performed in a part of the Meuse catchment, located in Limburg the most southern province of the Netherlands. In the study, 45 pharmaceuticals and 18 transformation products were studied in the Meuse, contributing streams and the "Lateraal Kanaal" (a canal parallel to the river Meuse) of which the water is used as source for drinking water production. The concentrations observed were high (up to tens of µg's) due to the high contribution of waste water effluents to this water system. It was found that an important part of the load entered the Netherlands from Belgium and France, However, also the wastewater treatment plants in Limburg significantly contributed to the concentrations and loads found in the Meuse and Lateraal Kanaal. Metformin and its metabolite guanylurea showed the highest concentrations in the Limburg water system. However, acute toxic effects of the analysed compounds are not to be expected for humans. Van der Aa et al. (van der Aa, 2011) have made a prediction of the increase in consumption of pharmaceuticals as a result of expected demographic effects. They predict that this consumption will increase by almost 40%, mainly caused by an increase in the number of elderly people [Ter Laak and Hofman, in prep.].As a result, concentrations in e.g. surface water will also increase. Even if at the moment no toxic effects are to be expected, in future this may be come a problem for e.g. drinking water production.

3.4 More information

More detailed information can be found in the following reports and peer reviewed papers:

- Thomas ter Laak, Monique van der Aa, Corine Houtman, Peter stoks, Annemarie van Wezel; Temporal and spatial trends of pharmaceuticals in the Rhine; RIWA report; febr. 2010
- T.L. ter Laak, M. van der Aa, C.J. Houtman, P.G. Stoks, A.P. van Wezel; Relating environmental concentrations of pharmaceuticals to consumption: a mass balance approach for the river Rhine; Environ.Int.36(5), 403-409; 2010
- Cindy de Jongh, Pascal Kooij, Thomas ter Laak; Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water; BTO 2011.045, 2011
- C.M. de Jongh, P.J.F. Kooij, P. de Voogt, T.L. ter Laak; Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water; Sci. Tot. Environm., 427-428, 70-77, 2012
- Appendix III

4 Veterinary pharmaceuticals

4.1 Occurrence of veterinary pharmaceuticals in the watercycle

So far, in most studies on pharmaceuticals veterinary pharmaceuticals have drawn less attention, even though the consumption volumes in the Netherlands are similar to the consumption of human pharmaceuticals. The type of pharmaceuticals used in veterinary practice clearly differs from the pharmaceuticals used in human medicine. While a major fraction of the human pharmaceuticals are anagetics/analgesics, medication against high blood pressure, hearth-diseases, high cholesterol, diabetics and all kinds of neurological disorders, veterinary pharmaceuticals are mainly antibiotics, anti-parasitics, and some anesthetics and tranquilizers.
However, part of the pharmaceuticals used in veterinary practice is also applied in human medicine so observed environmental concentrations of these pharmaceuticals might partially be of veterinary origin.
The consumption of veterinary pharmaceuticals differs between countries and between different livestock. It was found that the Dutch consumption of antibiotics per animal exceeds the consumption of all European countries, while the human consumption of antibiotics in the Netherlands is the lowest of all European countries. Consequently the veterinary consumption of antibiotics in the Netherlands exceeds human consumption by one order of magnitude. This is related to the size of stables and the structure of the Dutch veterinary industry.
The route of veterinary pharmaceuticals into the environment differs from human pharmaceuticals because veterinary manure/slurry is collected and often used as fertilizer on land, while excreted residues of human pharmaceuticals are transported to waste water treatment plants and potentially end up in surface waters. Figure 4-1 gives an overview of the transport of veterinary pharmaceuticals in the environment. Note that the manure of poultry is generally not applied on land, but exported or incinerated.

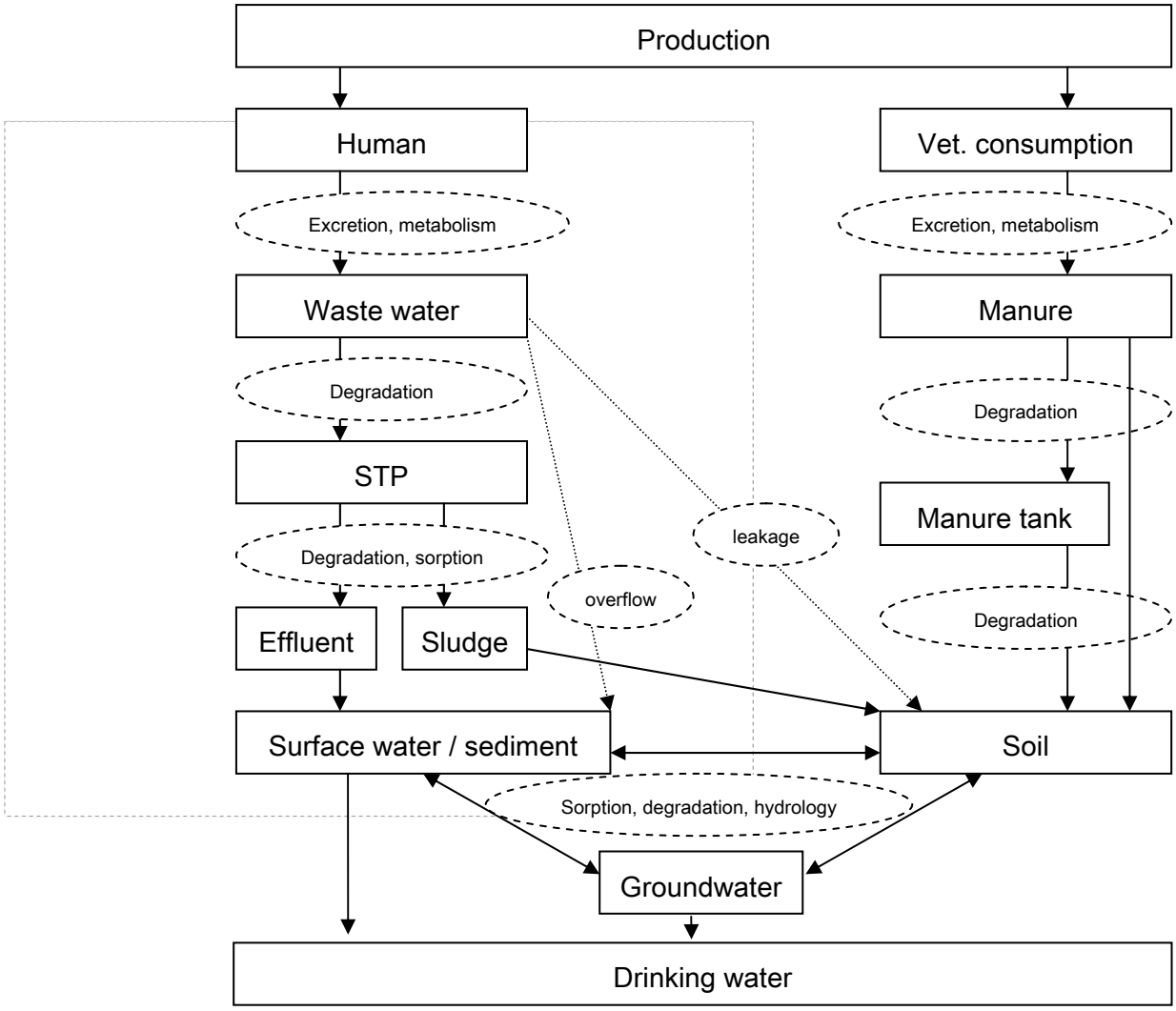

Figure 4-1: Fate of (veterinary) pharmaceuticals in the environment and potential transport to (sources of) drinking water. The circular boxes describe the processes that influence the fate of these chemicals between the different compartments.

90% of the pharmaceuticals used in veterinary practice are antibiotics. Despite of the prohibition of antibiotics as growth promoter, and the decreasing numbers of live stock, antibiotic use remained stable at over the last 10 years.

The sorption to soil sediment is an important aspect determining the fate of pharmaceuticals in the environment. Various studies have shown that the sorption of (veterinary) pharmaceuticals to soil and manure does not follow a clear relation with the commonly applied octanol-water partition coefficient. Generally applied models underestimate sorption by orders of magnitude. Antibiotics (and other pharmaceuticals) can sorb to soil by electrostatic interactions or complexation to both organic and inorganic phases in the soil or sediment. This inevitably means that the sorption process can be affected by aqueous chemistry (pH, ionic strength, valence of ions in solution, competing ions) as well as both organic and inorganic soil properties. This makes the prediction of sorption of these chemicals complicated. For surface waters the contribution of veterinary pharmaceuticals is considered rather small. However, the extraordinary high consumption of some antibiotics in Dutch veterinary practice might still result in relevant contributions for especially smaller surface waters in agricultural areas. Additionally, for groundwater the contribution of veterinary pharmaceuticals is probably more relevant than human consumption as practically all solid domestic waste and dried sludge of wastewater treatment plants is incinerated in the Netherlands, while manure is used as fertilizer.

The type of pharmaceuticals used in pet animals is far more diverse (more similar to what is used in human medicine) and their emission routes are more diffuse. Additionally, various antibiotics and anti-fungals are applied in fish farming. These chemicals likely end up in surface waters if the fish farms are in open connection with surface waters, if sediment sorption is low.
The fact that a very large amount of veterinary pharmaceuticals is used, the major part of which eventually will end up in the environment, makes it necessary to include these pharmaceuticals in legislation. However, this will require efficient monitoring of at least part of these compounds.

4.2 Screening for veterinay pharmaceuticals and metabolites in groundwater

This subproject focused on the occurrence of (veterinary) pharmaceuticals in groundwater used for the production of drinking water. As agricultural land is usually fertilized with manure that can contain veterinary pharmaceuticals, groundwater in agricultural areas might also contain pharmaceuticals. Samples were taken at seven different locations, based on land use and soil conditions. The locations are shown in Figure 4-2.

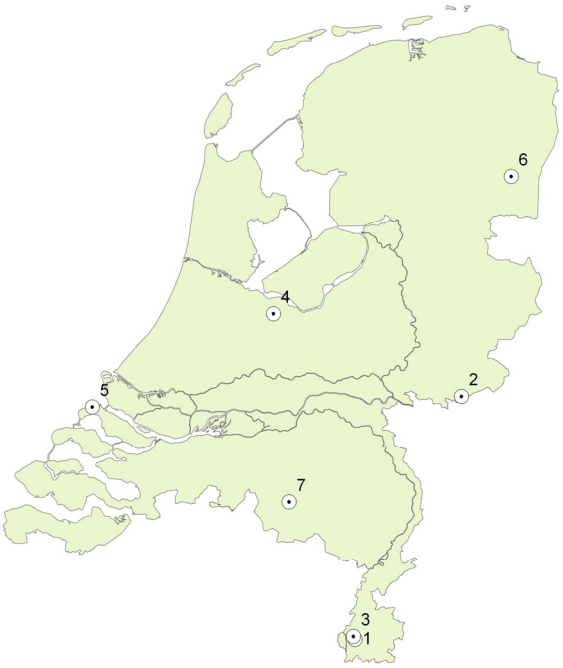

Figure 4-2: Sample locations

It was shown that pharmaceuticals can pass soil when surface water is infiltrated, and that residues of pharmaceuticals can be found several decades after infiltration of sewage was applied, illustrating the persistence of certain pharmaceuticals in soil. Especially polar neutral pharmaceuticals seem to be mobile in soil and may end up in groundwater. Positively of negatively charged pharmaceuticals are leaching to a lesser extent and are not observed in groundwater, despite of their high aqueous solubility.

Despite the selection of locations and monitoring wells, none of the veterinary pharmaceuticals (antibiotics) have been observed in the superficial groundwater. Many (veterinary) antibiotics, such as tetracyclins, quinilones and macrolides strongly sorb to soil, and therefore could not be detected in groundwater. Additionally, penicillins are unstable under environmental conditions, and therefore also hardly are found in aqueous environments. Sulfonamides and trimethoprim are weakly adsorbed by soil, and their occurrence in surface waters and occasionally in groundwater has been described in literature. However, the majority of these observations are from the US, where groundwater was sampled near manure lagoons containing high loads of veterinary pharmaceuticals. In the Netherlands

manure is more or less evenly distributed over fields after considerable storage in tanks, resulting in more equally distributed, lower concentrations in groundwater.
No concentrations above the threshold of toxicological concern (TTC) were observed in the sampled drinking water, although concentrations of some compounds slightly exceeded this level in groundwater. Based on the results of this screening campaign at the moment no adverse health effects of the studied compounds are expected in (sources of) drinking water in the Netherlands.

4.3 Antibiotic resistance genes in the environment

Resistance genes are of all ages, so the question rises whether the observed occurrence of antibiotic resistant pathogens is related to consumption of antibiotics. It was found that amounts of resistance genes for tetracyclins, β-lactams and erythromycins significantly increased in various Dutch soils since the 1940s. These observations provide evidence that the increasing consumption of veterinary antibiotics leads to changes in the gene reservoirs of the soil. Additionally, it was shown that elevated levels of resistance genes remained present in field soils even when the soil was not exposed to manure containing antibiotics and resistance genes for several years. Bacterial communities in soils, pre-exposed to veterinary antibiotics, revealed higher tolerance towards antibiotics that were not pre-exposed. Thus, resistance genes may be included and maintained within the gene pool of the bacteriological community. Additionally, the presence of tetracycline resistance genes in groundwater suggests that these genes have leached from the top soil (although they were not detected in groundwater, probably as a result of adsorption to the soil). Part of this increase might be related to the consumption of antibiotics in veterinary practice and aquacultures, as epidemiologic studies showed a correlation between the increase in the occurrence of resistant strains in veterinary practice and humans.

4.4 More information

More detailed information can be found in the following reports:

- Thomas ter Laak, Leo Puijker, Annemarie van Wezel; Veterinary Pharmaceuticals in drinking water sources; a first inventory; Nov. 2010
- Thomas ter Laak; Wetgeving voor Diergeneesmiddelen en de relevantie voor de watersector; notitie; Dec. 2010
- Thomas ter Laak; Mobility of antibiotic resistance genes in the environment and potential threats for drinking water; BTO 2012.022; Aug. 2012
- T. ter Laak, P. Kooij; Screening for pharmaceuticals and metabolites in groundwater; BTO 2012.227 (s); Aug. 2012
- Appendix IV.

5 Removal by means of nanofiltration

Membrane filtration may represent a cost-effective solution to tackle the occurrence of pharmaceuticals in drinking water sources as high removal efficiencies of micro-pollutants have already been found [Bellona et al., 2004; Kimura et al., 2003 and 2004]. Nanofiltration can be applied for the removal of salts, particles, pathogens but also organic micro-pollutants. However, in order to fully exploit its potential, the underlying mechanisms of rejection need to be understood, especially under realistic operating conditions, namely in the presence of fouling constituents in the feed water. The research conducted at KWR aimed at providing insight into the process of membrane filtration and its rejection behavior for a wide range of micro-pollutants by combining pilot testing with comprehensive membrane characterization.

5.1 Removal efficiency and effects of fouling

The removal of lower molecular weight (MW) pharmaceuticals in NF installations might, in some cases, not be complete, even though the MW is larger than the molecular weight cut off (MWCO) of the membranes [Bellona et al., 2004]. In general, the MWCO of the membrane is used to indicate the lower limit of molecules that cannot pass the membrane. However, other rejection mechanisms like hydrophobicity and charge interactions also play an important role in governing removal efficiencies [Bellona et al., 2004; Verliefde et al, 2008]. As the physico-chemical interplay between the membrane and the micro-pollutants regulates membrane rejection, the characterization of these interactions becomes fundamental to develop the most suitable barrier against pharmaceuticals in drinking water.
Another important aspect to be considered is that, while operating a membrane installation, fouling problems might arise that could partially deteriorate the quality of the produced water. Due to the deposition of particles, salts, colloids and/or bacteria in time, the membrane surface will also be altered. This modification of membrane surface properties may lead to changes in solutes removal, as the above mentioned rejection mechanisms (steric exclusion, charge interactions and solute-membrane affinity) are largely governed by membrane surface properties [Flemming et al., 1997; Bellona et al., 2004]

In order to assess the efficiency of membrane filtration in the removal of pharmaceuticals the following aspects were tackled with the present research:

- removal efficiency of a mixture of low molecular weight pharmaceuticals varying in size, charge and hydrophobicity;
- understanding the underlying rejection mechanisms by performing membrane surface characterization;
- investigating whether occurrence of biofouling could result in modified rejection efficiencies.

Experiments were carried out in a pilot plant, consisting of two parallel membrane pressure vessels.

Nanofiltration can efficiently remove a broad range of diverse organic micro-pollutants. The removal was on average equal to 93% and 90% for clean and biofouled membrane respectively (figure V-3). Higher rejection values were generally observed for negatively charged pharmaceuticals compared to neutral and positively charged solutes. This behavior can be ascribed to the negative charge of the membrane surface that results in charge repulsion for negatively charged pharmaceuticals and in the accumulation of positively charged solutes on the membrane surface. Upon biofouling, a highly hydrated biofilm developed onto the biofouled membrane, conferring a higher hydrophilicity to the membrane. This modification had a negative impact on the rejection of more hydrophobic solutes, but a beneficial effect for small hydrophilic ones (like glycerol) [Botton et al., 2012].

Nanofiltration experiments conducted in this research were operated at a system recovery of 10%. Full-scale membrane systems for ground or surface water operate at much higher recoveries ranging between 75%-85%. At higher recovery values the solute concentration is higher in the membrane elements, and it is known that this will result in lower rejection values. The expected pharmaceuticals rejection values on

full-scale NF are therefore lower than the determined pharmaceuticals values on bench-scale. For solutes with a rejection of 85% at 10% recovery, the rejection decreases to 70% at 80% recovery [Verliefde et al., 2009]. In this study this means that for a virgin NF membrane, the rejection of propanolol, phenazone and sulfamethoxazole on full-scale NF is expected to be lower than 80%. For the other investigated compounds the rejection on full-scale is expected to be higher than 80%. In the case of severe biofouling especially the positively charged pharmaceuticals will be affected, resulting in an expected drop in rejection of particularly smaller, positively charged and hydrophobic solutes such as pindalol (relatively hydrophobic, positively charged), proponolol (hydrophobic, positively charged) and phenazone (small). In such a case, application of only nanofiltration may not be sufficient.
A high pressure membrane process, such as reverse osmosis (RO), can also be applied to reject pharmaceuticals from drinking water sources. RO membranes are very dense and form a robust barrier for the rejection of emerging substances, such as pharmaceuticals, from groundwater or surface water. The major disadvantage of these membranes is the relatively high pressure which is required to facilitate sufficient water transport through the membrane. NF membranes are more open compared to RO membranes and thus require less energy. The balance between pharmaceuticals rejection and energy requirement will depend on the specific water quality of the source water.

5.2 More information

A more detailed description of the experiments and results is shown can be found in:

- Sabrina Botton, Emile Cornelissen; Removal efficiency of pharmaceuticals in drinking water production; Application of nanofiltration; BTO 2012.008(s); 2012
- Appendix V

6 Conversion by means of LP UV/H_2O_2 processes

6.1 Experiments in Collimated Beam set-up and in pilot plant

UV/H_2O_2 processes belong to the category of "advanced oxidation processes". These are processes in which the highly reactive hydroxyl radical is formed, which can oxidize a wide range of organic compounds. In this specific case, two reactions can take place simultaneously: photolysis by absorbed UV irradiation, and oxidation by hydroxyl radicals, formed upon photolysis of the H_2O_2 present. In general two types of UV lamps can be used for this process: medium pressure (MP) and low pressure (LP) UV lamps, both containing mercury. In a previous BTO project [IJpelaar et al., 2010; Hofman-Caris and Beerendonk, 2011a] it was shown that application of UV irradiation in combination with hydrogen peroxide oxidation, is effective in converting a broad range of organic micropollutants. In that project, conversion and efficiency for three different UV lamps were compared:

- Medium Pressure (MP) UV lamps, with a "broad" UV spectrum between 200-400 nm, a "high" power but a relatively low efficiency
- Low Pressure (LP) UV lamps, which emit UV light at a wavelength of 253.7 nm, have a relatively low power but a high efficiency
- Prototype Dielectric Barrier Discharge (DBD) lamps, with a small UV spectrum (220-270 nm, with a maximum at 242 nm), which combine a high power and a high yield.

It was concluded that systems equipped with LP UV lamps in general require the smallest amount of energy for conversion of a broad range of micro-pollutants in UV/H_2O_2 processes.

Based on the conclusions from this previous project, it was decided to study the conversion of a large number of pharmaceuticals by means of a UV and a UV/H_2O_2 process. This study was carried out in two experimental runs:

1) Collimated beam experiments in order to check whether it would be possible to analyze the conversion of the pharmaceuticals as a result of a UV or a combined UV/H_2O_2 process. Furthermore, it was checked whether by-products, that may be formed during the photolysis or oxidation of the pharmaceuticals, or metabolites may interfere with the laboratory analysis of the parent compounds. Finally, it was determined whether or not the addition of Na_2SO_3 to stop the direct reaction with H_2O_2 after irradiation (called quenching) interferes with the analysis of the compounds, i.e. whether it is necessary to quench the reaction.
2) Experiments with the LP pilot plant of Dunea (which also had been used in the previous project), but now for a large range of pharmaceuticals.

A picture of the experimental set-up is shown in appendix IV.

By means of collimated beam experiments, it was shown that metabolites of the pharmaceuticals, as found in sources for drinking water, are not formed during the UV/H_2O_2 process. Besides, their presence does not interfere with the analysis of the compounds.
Furthermore, it was shown that the effect of compounds reacting with only H_2O_2 is very small, and that addition of Na_2SO_3, in order to quench this reaction, may interfere with the analysis of the compounds. Therefore, it was decided not to quench the samples after the reaction.

As expected, the efficiency of the UV photolysis process strongly depends on the molecular structure of the compounds involved. However, when photolysis is combined with oxidation by hydroxyl radicals, formed by means of photolysis of H_2O_2 added to the mixture, the majority of compounds appear to be efficiently degraded. An overview of conversions obtained with the LP pilot reactor at Dunea, using pretreated Meuse water, is shown in Table 6-1.

Table 6-1: conversion efficiency of the Dunea LP reactor at 100% power ballast setting

compound	≥ 80%	60-80 %	20-60%	< 20 %
AMPH	x			
atenolol			x	
bezafibrate		X		
carbamazepine		X		
ciprofloxacine				
clenbutarol	x			
clindamycine		X		
Clofibric acid		X		
cortisol	x			
cortisone		X		
cyclophosphamide				x
diatrizoic acid		X		
diclofenac	x			
dimethylaminophenazone	x			
erytromycine A			x	
fluoxetine	x			
furosemide	x			
gemfibrozil		X		
guanylurea				x
ifosfamide			x	
ketoprofen	x			
lincomycine		X		
metformine				x
metoprolol		X		
metronidazole			x	
naproxen		X		
niacin			x	
paracetamol	x			
paroxetine	x			
pentoxifylline			x	
phenazone	x			
pindolol	x			
prednisolone	x			
propranolol	x			
salbutamol		X		
sotalol	x			
sulfachloropyridazine	x			
sulfadiazine	x			
sulfamethoxazole	x			
sulfaquinoxalin		X		
terbutaline			x	
trimethoprim		X		
venlafaxine		X		

An indication on the amount of energy required to obtain 90% conversion (in a certain reactor and water quality) is given by the E_{EO} value (Electrical Energy per Order, kWh/m^3). The results obtained in the LP pilot reactor of Dunea are shown in Appendix IV. It should be kept in mind, that the pretreated Meuse water used in this experiment has a relatively low UV-transmittance (about 74%), as a result of which the E_{EO} in this case will be relatively high. It was found that only the conversion of some small, hydrophilic

compounds (like metformine and guanylurea) will require a disproportionate amount of energy. However, it will be an economical consideration, whether such compounds will have to be degraded in this way, or whether an additional process step will be more efficient for their removal.
Besides, the energy demand also strongly depends on the reactor geometry and flow conditions in the reactor. Whether or not a UV/H_2O_2 process in a certain case will be (economically) feasible will depend on the actual conditions, and will have to be established for each individual case. Furthermore, the effects of possible byproducts that may be formed during the process will have to be studied. Removal of such byproducts may require an additional process step, like filtration over activated carbon.

6.2 More information

Full details on this sub-project can be found in:

- C.H.M. Hofman-Caris, B.A. Wols, D.J.H. Harmsen; Removal efficiency of pharmaceuticals in drinking water production; Application of UV/peroxide oxidation; BTO 2012.211(s); 2012
- Appendix VI

7 Adsorption processes: applicability of affinity adsorption

7.1 Polymer adsorbents versus activated carbon

For this part of the project, five different polymer adsorbents and powdered activated carbon (PAC) were compared. Adsorption is defined as the adhesion of molecules to a surface. Several forces can be involved in the adsorption of a compound, like Van der Waals and Coulomb forces, hydrogen bonding (including base pairing), acid-base interactions and pi-stacking (for compounds containing aromatic structures) Affinity adsorption uses highly selective interactions between structural elements in the compounds and functional groups at the adsorbent surface [de Graaff et al., 2011]. As pharmaceuticals have been designed to show specific interactions within living organisms, they often contain special functional groups. By using the presence of these groups, it may be possible to apply specific polymeric resins, also containing special functional groups, to adsorb certain categories of pharmaceuticals, with comparable functionalities.
The polymer resins used in this investigation all were based on Oasis HLB, with a backbone consisting of apolar moieties (benzyl groups, aliphatic chains) and polar groups (pyrrolidone). This backbone can carry different types of surface modifications, as shown in figures 3.1 and 3.2.

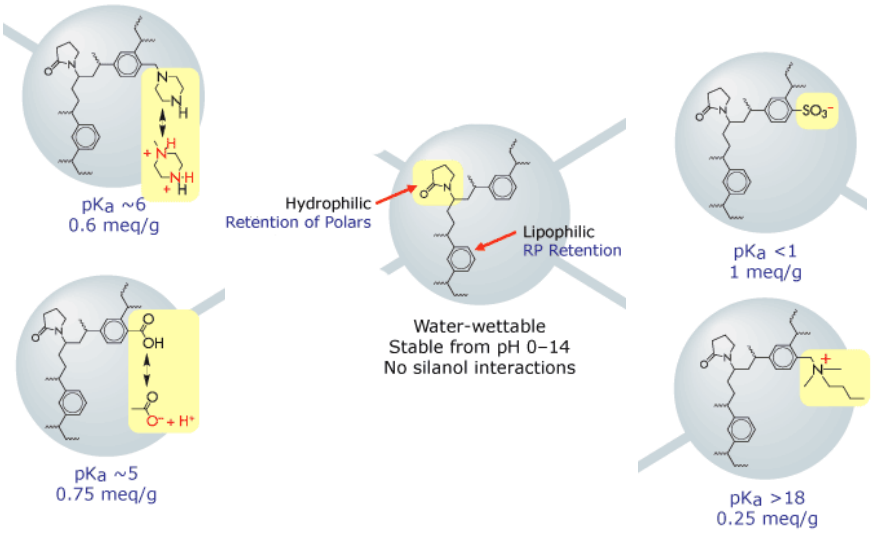

Figure 7-1: OASIS materials, made by Waters (source: http://www.waters.com/waters/)

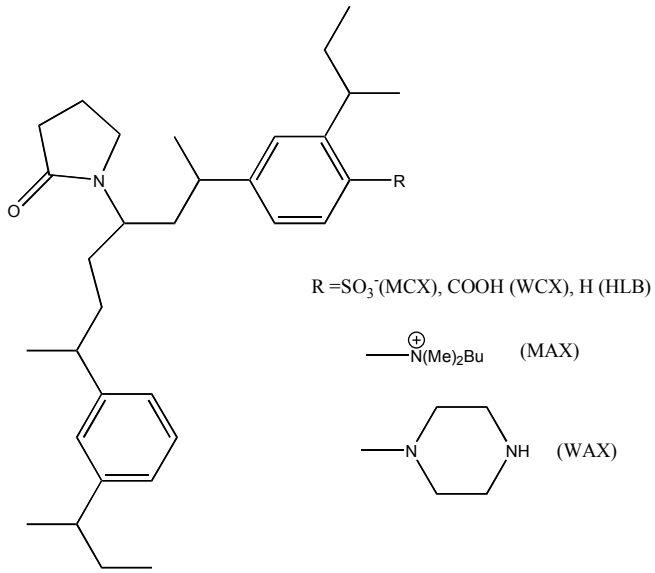

Figure 7-2: Backbone of the OASIS materials and the functional groups applied

- Type HLB consists of only the backbone material, and is capable of hydrophobic interactions
- Type WAX contains 0.55 mmol piperazine/g; it is positively charged and can form hydrogen bridges
- Type WCX contains 0.74 mmol carboxylic acid/g; it is negatively charged and can form hydrogen bridges
- Type MAX contains 0.31 mmol ammonium/g; it is positively charged, but cannot form hydrogen bridges
- Type MCX contains 1.01 mmol sulfonic acid/g; it is negatively charged, but cannot form hydrogen bridges

Experiments were carried out in MilliQ water, and in Nieuwegein drinking water, in order to study the effect of the presence of natural organic material (NOM), which is present in Nieuwegein drinking water, but not in MilliQ water.

For each adsorbent a mixture of pharmaceuticals was used. For this purpose pharmaceuticals with certain functional groups were chosen, which were expected to be able to interact with the adsorbent surface. In all cases, the adsorption was compared with the adsorption on PAC. The results are shown in Appendix VII.
It was concluded that it is possible to use affinity adsorption to remove a certain compound or category of compounds from an aqueous solution, based on their molecular structure in combination with e.g. pH. Oasis polymer resins, known for their analytical applications, appear to be very effective adsorbents in column experiments. Affinity adsorption seems to be less depending on competition with NOM, as it involves very specific interactions. This is an advantage, but it may also be a disadvantage, as affinity adsorption probably will not be suitable as a robust purification method for a wide range of pharmaceuticals (although it may be very suitable for e.g groundwater or wastewater with only a limited amount or special category of compounds that has to be removed). If adsorption is to be used as the main technology, different resins will have to be used in a cascade of processes (or possibly in a mixed bed). It is more likely, that affinity adsorption will be applied as a polishing step, in order to remove compounds that are very hard to remove otherwise.
PAC is a very effective adsorbent, although with PAC the competition with NOM plays a more important role, rendering the adsorption less effective. Also, it was observed that PAC is less effective for small, charged compounds. In these experiments no breakthrough curves have been determined, so no conclusions can be drawn on the possible break through of pharmaceuticals on polymer resins.

Another topic that has not been addressed yet, are the regeneration possibilities for the polymer resins. The economic applicability of affinity adsorption processes will strongly depend on how often the material will have to be regenerated, how much energy this will cost and which of type and amounts of chemicals will have to be involved.
Furthermore, at the moment such polymer resins are not yet available on a large scale. However, in this part of the project a proof of principle for affinity adsorption was given. For applications on a plant scale, it will be worthwhile to investigate the possibilities to use alternative, low cost, carriers, like hydro talcite, clay derivatives, or zeolites. For these materials too, the matter of regeneration possibilities will have to be addressed.

7.2 More information

More detailed information on this part of the project can be found in:

- C.H.M. Hofman-Caris, W.G. Siegers; Removal efficiency of pharmaceuticals in drinking water production; Application of affinity adsorption techniques; BTO 2012.010(s); 2012
- Appendix VII.

8 Developing QSARs

The efficiency of water treatment systems to remove emerging substances (like pharmaceuticals) from sources of drinking water often is unknown. It would be very helpful if e.g. from the molecule's structure, predictions could me made. A promising approach is using QSARs (quantitative structure-activity relationships) to link the existing knowledge on a compound's chemical structure to water treatment process properties.
QSARS are not widespread in water treatment, probably because of a lack of consistent available data. It was tried to use the data gathered in this research in order to develop QSAR models for nanofiltration and the UV/H_2O_2 process.
Two approaches were followed: a knowledge-based and a data-based approach.

8.1 Knowledge-based QSARs

The knowledge-based approach uses QSAR models to predict physico-chemical constants of emerging contaminants. A statistic relation is calculated between certain structural features of molecules and their known physico-chemical constants. This is called the "training of the QSAR". The statistic relation then is applied to estimate unknown physico-chemical parameters of other compounds, based on their structural features. The applicability of the QSAR (statistic model) is checked by applying it to molecules with known parameters within the same data set, in order to see whether the predicted values are in good accordance with the actual values. Furthermore, an external validation test should be carried out, by repeating this procedure with compounds whose parameters are known in literature (but were not part of the same data set that was used to train the QSAR).
These physico-chemical constants have to be used as input parameters in a process model, in which compound conversion or removal can be calculated. The process model uses information about the treatment process (like process conditions and reactor configurations), parameters describing the water matrix (for example UV-T and concentrations of background substances relevant for UV/H_2O_2 processes), and physico-chemical properties of the compounds of interest. Process (efficiency) models already exist for most water treatment processes. For example, the rejection of organic compounds by nanofiltration membranes can be predicted by convection-diffusion transport models [Verliefde et al., 2009], and the degradation of organic compounds by UV/H_2O_2 processes can be predicted by (photo-) chemical reaction models [Hofman-Caris et al., 2011b and 2012a; Wols et al., 2011]. However, these models require physico-chemical properties (for example reaction rate constants), which are often unknown. By applying a QSAR model these parameters can be estimated, based on the molecular structure of the compounds. For the training of the QSAR, these properties are estimated from data of dedicated small-scale experiments, or they are estimated from the process models by assuming all other properties known and using the measured removal rates. Full details can be found in [Wols et al., 2012b].
The most important physico-chemical properties for the UV/ H_2O_2 process are quantum yields [Ohura et al., 2008], molar absorptions and reaction rates with hydroxyl radicals [Kusic et al, 2009].

For the hydroxyl radical reaction rate, the following QSAR model was obtained:

$$\log y = 0.99 - 0.56 qCmean - 0.34 BELv1 - 0.42 ATS2m + 0.66 piPC03, \quad (1)$$

training data: $n = 122$, $R^2 = 0.774$, $F = 100$, $Q^2_{LOO}=0.735$, $SD_{res} = 0.062$
test data: $n = 25$, $Q^2_{ext}=0.584$, $F = 13$, $SD_{res} = 0.049$

where $\log y$ is the (log normalized) reaction rate of OH radicals

The best fitting descriptors are the electronic charges on a C atom [qCmean: mean charge on C atoms], and topological information about the size of the molecule and the distance between atoms [BELv1: the lowest eigenvalue nr 1 of Burden matrix, weighted by atomic van der Waals volumes; ATS2m: the Broto-Moreau autocorrelation of a topological structure-2 weighted by atomic masses; piPC03: molecular

multiple path count of order 3. a negative correlation was found between qCmean and the OH radical reaction rate].
Although a good QSAR ($R^2 > 0.7$, $Q^2_{ext} > 0.5$) was found for hydroxyl radical rate constants, only moderate QSARs ($0.5 < R^2 < 07$) could be found for the other physico-chemical parameters used in the process model (quantum yield and molar absorption). Furthermore, the moderate QSAR models did not pass the external validation tests ($Q^2_{ext}<0.5$). As a broad range of pharmaceuticals was used, a wide variety of chemical reactions will have been caused by absorption of UV irradiation, based on a wide variety of structural features. Thus, it will hardly be possible to find a limited amount of descriptors which play an important role in all photolysis reactions. This problem may be overcome by defining descriptors for sets of structurally strongly related compounds, but in that case the challenge will be to obtain sufficient experimental data.

For the nanofiltration process, most suitable endpoints would be surface tensions of compounds, because they only depend on the compound, and not on the membrane. However, only limited data of surface tensions are available. Therefore, the partition coefficient is used as an alternative endpoint. Such a QSAR is only valid for a single membrane. Prior to the training of the QSAR model, the membrane pore size and thickness have to be fitted from measured data. This, however, appeared to result in large differences between measured and fitted data,. The large uncertainties in the process model thus are responsible for the fact that the knowledge-based QSAR models could not be developed for NF.

8.2 Data-based QSARs

In the data-based approach, a QSAR model is constructed that directly predicts the compound's removal by a water treatment process. So, the process conditions as well as the compound's chemical structure are captured in several descriptors that correlate to the compound removal. The data-based approach has a narrow prediction range, since it is trained in a specific experimental environment. Moreover, deviations of the model can not be understood easily, because physical and/or chemical knowledge of the process is not included in the QSAR approach. Figure 8-1 schematically shows the data-based QSAR approach.

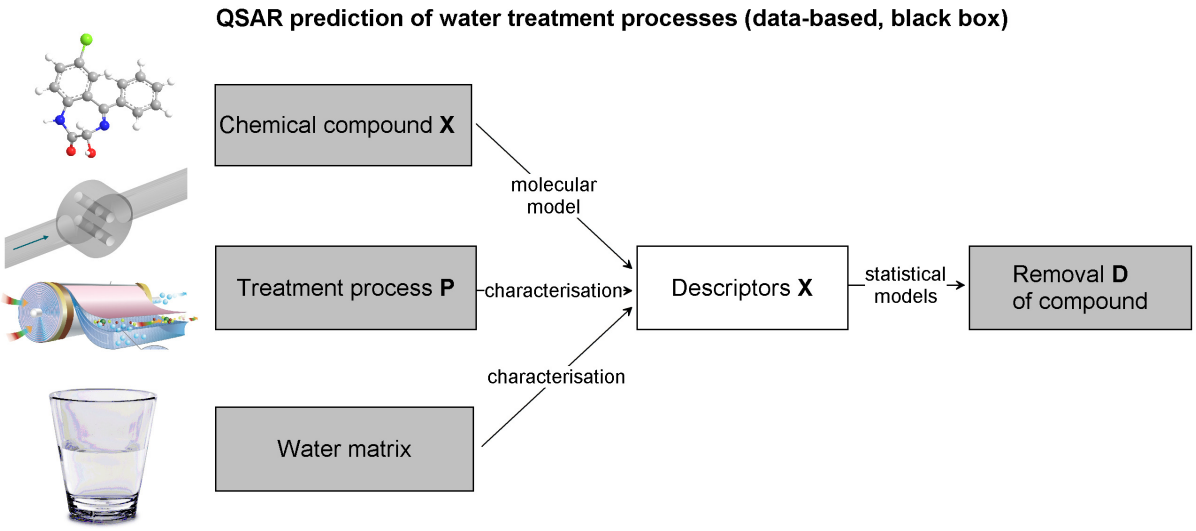

Figure 8-1: The data-based (black box) QSAR approach to predict the removal of priority compounds by water treatment processes

The data-based QSARs for UV/H_2O_2 were trained with data obtained from the pilot plant of Dunea in Bergambacht. The log degradation after UV/H_2O_2 treatment of water in the pilot plant of Dunea is considered as endpoint. The best fitting QSAR model is selected and results in:

$$\log y = -0.162 + 3.934xch9 - 0.3824\ GATS6v - 0.06287ALOGP2 + 0.5587\ O\_aromatic\_attach, \quad (2)$$

training data: $n = 32$, $R^2 = 0.591$, $F = 10$, $Q^2_{LOO}=0.268$, $SD_{res} = 0.265$
test data: $n = 3$, $Q^2_{ext}=-0.023$, $F = 0$, $SD_{res} = -$

where y is the degradation in the UV/H_2O_2 reactor.
The descriptors are related to molecular information [*ALOGP2*: Ghose-Crippen octanol water coefficient squared], structural information [*O_aromatic_attach*: number of O atoms attached to an aromatic ring], topological information [*xch9*: the 9th chi connectivity index, *GATS6v*: Geary autocorrelation - lag 6 / weighted by atomic van der Waals volumes].

This QSAR model was validated by a small set of test data and external data, both showing its low predictability. This probably can be attributed to the wide variety of photochemical reactions that can take place, especially within a set of molecules characterized by various different structural elements.

In order to develop data-based QSARs for nanofiltration, virgin membranes were considered. The equation for the QSAR model obtained is:

$$\log y = 2.023 + 0.02616\ SssO - 0.894\ iddmm + 0.09196\ nAB - 1.068\ COOH, \quad (3)$$

training data: $n = 40$, $R^2 = 0.884$, $F = 72$, $Q^2_{LOO}=0.857$, $SD_{res} = 0.202$
test data: $n = 23$, $Q^2_{ext}=0.784$, $F = 19$, $SD_{res} = 0.258$

where y is the membrane rejection. The descriptors are related to: molecular information [*nAB:* number of aromatic bonds], structural information [*COOH*: number of COOH groups in the compound to an aromatic ring, *SssO:* Sum of (– O –) E-States], topological information [*Iddmm:* Mean information content on the distance degree magnitude].

This model was validated using an external data set of 23 compounds. The internal predictability of this QSAR model seemed to be high ($R^2 > 0.8$, $Q^2 > 0,9$).

8.3 Prediction by means of QSAR models

The QSAR models developed for UV/ H_2O_2 and NF are summarized in Table 8-1 and Table 8-2. A moderate ($R^2>0.5$) to good ($R^2>0.7$) correlation has been found for the training data (Table 8-1). However, when the QSAR models are tested with an external data set (Table 8-2), not all models pass this test. This underlines the importance of external validation. Only the data-based QSAR model for Desal HL membranes and the knowledge-based QSAR model for hydroxyl radical rate constants seem to be reliable ($Q^2>0.5$). This can be explained by the nature of the process and the available data.

*Table 8-1: Overview of predictability of QSAR models for **training** data. Green: $R^2>0.7$, Orange: $R^2 > 0.5$, Red: $R^2<0.5$.*

	Data-based QSAR models	Knowledge-based QSAR models
UV/ H_2O_2	LP reactor at Dunea	Hydroxyl radical reaction rate
		Quantum yield
		Molar absorption
NF	Desal HL membranes	-

*Table 8-2: Overview of predictability of QSAR models for **external** data. Green: R^2>0.75, Orange: R^2 > 0.5, Red: R^2<0.5.*

	Data-based QSAR models	Knowledge-based QSAR models
UV/ H_2O_2	LP reactor at Dunea	Hydroxyl radical reaction rate
		Quantum yield
		Molar absorption
NF	Desal HL membranes	-

The large variability in type of compounds may result in a large domain of applicability, so that the QSAR model would be valid for a wide range of compounds. Nevertheless, such a wide range may also cause many different (chemical) mechanisms of action, which may be difficult to capture in a few descriptors. As a result, the number of compounds per mechanism of action may in fact be too low to obtain a reliable QSAR model.
Regarding the nature of the process, for nanofiltration processes it is known that the size and shape of the molecule as well as the hydrophobicity are important factors that define the rejection. Therefore, good correlations have been found between rejection and topological descriptors as well descriptors related to hydrophobicity, such as the number of COOH groups present in the molecule. For UV oxidation, a broad variety of reaction mechanisms may cause transformation of pharmaceuticals (Klán and Wirz, 2009). Especially UV photolysis is very hard to predict, as it is a very selective process, in which various kinds of chemical bonds may be attacked by the photons. As reactions take place from an excited state, they very often don't follow "normal" reaction rules, making predicting even more complicated. Such a large number of mechanisms of action cannot be represented by only a few descriptors. As a result a satisfactory QSAR could not been found for the quantum yield and molar absorption. This may be improved by defining QSARs for structurally strongly related sets of compounds, although it will be difficult to obtain sufficient data for a reliable QSAR for each set. Moreover, these specific QSARs have a much lower domain of applicability, so that they can only make predictions for a small range of compounds. Besides, it will be a challenge to apply these QSARs to compounds like pharmaceuticals, which may well contain more than one functional group.

The QSAR models developed in this project were used to predict compound removal in water treatment systems. Some results are shown in Appendix VIII. From figure VIII-1 it can be concluded, that for nanofiltration a good agreement is found between measured and predicted data, except for trimethoprim, paracetamol and metformin. However, it should be kept in mind that this QSAR is only valid for Deal HL membranes. The knowledge-based approach could not be followed due to uncertainties in the process model.

For the UV/H_2O_2 process, good predictions were obtained using the knowledge-based QSAR for the oxidation reaction (k_{OH}), especially at a ballast setting of the UV lamps of 100%. The latter probably is explained by the fact that the ballast percentage may not be linear with the UV output. In general, the model seems to predict rather accurately the variability in compound degradation.
For the data-based approach and for the knowledge-based quantum yield and molar absorption only moderate QSAR models were found, which did not pass external validation tests (Q^2_{ext} < 0.5). This underlines the importance of external validation, by stressing that without external validation there is a serious risk of over fitting the model. Without a validation by external data sets there will be no guarantee that a QSAR model will be accurate for predicting the removal capacity of new compounds.

8.4 More information

More detailed information on the development and applicability of QSARs for pharmaceutical removal from water can be found in:

- Wols, B.A., Vries, D., Hofman-Caris, C.H.M., Removal efficiency of pharmaceuticals in drinking water production; application of QSARs, BTO 2012.228(s) (2012b)
- Appendix VIII

9 Comparison of different treatment techniques

9.1 Introduction

This research project showed that a large part of the pharmaceuticals prescribed (and their metabolites) soon or later enter the environment, and will be found in surface or ground water. Waste water treatment processes in general are not designed to deal with such compounds, and depending on their structure and concentration, they may also become a problem for drinking water purification processes. During recent years several technologies have been developed to deal with organic micropollutants, like e.g. membrane filtration processes, adsorption techniques and advanced oxidation processes. QSARs can be useful, in giving insight in the possibilities of a treatment technique in combination with the compound's chemical structure. However, in Chapter 8 it was shown that care has to be taken in developing and using QSARs for prediction of a compound's degradation or removal.
Apart from the possible efficiency of a treatment technique for a certain organic micropollutant (c.q. pharmaceuticals) also other, more practical, factors have to be taken into account, in assessing the applicability of a treatment technique. These aspects are dealt with in the present chapter.

9.2 Membrane processes

The pressure required in membrane filtration processes can be considered as the main energy requirement for this technique. According to literature [Fritzman et al., 2007], nanofiltration for ground and surface water in general requires less than 0.3 kWh/m^3, whereas for reverse osmosis this would be less than 1.0 kWh/m^3. This is due to the fact that RO membranes are very dense and thus require a high pressure to facilitate sufficient water transport through the membrane. NF membranes have a more open structure, and thus require less energy. The balance between pharmaceuticals rejection and energy requirement will depend on the specific water quality of the source water.

(Bio)fouling can cause several operational problems, like an increase in hydraulic resistance to permeate flow (leading to flux decline), higher frictional resistance of the membrane (resulting in a transmembrane pressure drop, affecting the energy demand of the installation), and hindered back diffusion of salts (resulting in elevated osmotic pressures at the membrane surface) [Flemming et al., 2002; Herzberg and Elimelech, 2007]. These mechanisms have a direct and tangible effect on the performance of full scale-membrane plants and ultimately lead to increased maintenance costs, for example due to the need of cleaning procedures to reduce flux decline. Although the effects of hydraulic parameters in general are well understood, the influence of biofouling on rejection performance had not yet been studied in detail. A lower rejection of pharmaceuticals may imply that membranes will have to undergo more frequent or different clean in place procedures. Such a lower rejection caused by biofouling indeed was observed for positively charged pharmaceuticals, whereas for neutral and negatively charged pharmaceuticals hardly any effect could be observed. Therefore, the removal efficiency of small positively charged and hydrophobic pharmaceuticals should be carefully monitored in full-scale installations, as this class of organic micro-pollutants presents the lowest rejection in NF membranes and appears to be the most susceptible to a further rejection decrease as a consequence of biofouling development. If the water source contains (a relatively high concentrations of) such compounds, it should be considered whether NF will be the most convenient process, or whether other processes, or a combination with other processes, would be preferred.

An important aspect of membrane filtration processes, which was not addressed within the scope of this project, is dealing with the concentrate. Application of membrane filtration inevitably results in the formation of a concentrate, which, at a recovery of about 80%, represents 20% of the influent, and will

have to be disposed off. The possibilities to deal with this concentrate largely affect the applicability of membrane processes in each individual case.

9.3 UV/H_2O_2 processes

For UV/H_2O_2 processes, the main energy demand is related to the UV dose that is required to obtain sufficient conversion of the organic micropollutants. In general, a dose of about 500-600 mJ/cm^2 will be applied for such a process. The energy required to obtain a sufficiently high UV dose strongly depends on the water quality (UV-transmittance) and on the flow conditions inside the reactor (determining how much UV irradiation the pollutants will receive upon passing the reactor). A good estimate of reactor efficiency can be obtained by applying Computational Fluid Dynamics (CFD) to the reactor [Wols et al., 2011]. The water quality also implies the presence of radical scavengers like (hydrogen) carbonate ions, which may interfere with the oxidation efficiency. Kinetic modeling of the process, taking into account such factors, in combination with CFD models, can give a good impression of the efficiency of a UV/H_2O_2 process for the conversion of organic micropollutants.
For most pharmaceuticals in this research, an energy demand of less than 1 kWh/m^3 was observed, which is in the same order of magnitude as what is required for membrane filtration processes. However, for some types of molecules (especially small, hydrophilic ones like metformine and guanylurea) a disproportionate amount of energy will be required to obtain sufficient conversion. In case the water contains a relatively high concentration of such compounds, it would be worthwhile to consider application of another technique, or combination of this technique with e.g. (affinity) adsorption processes.

An important factor in UV/H_2O_2 processes is the choice of UV lamps. "Traditionally" two types of lamps can be applied: Low Pressure (LP) and Medium Pressure (MP) UV lamps. Both types of lamps contain mercury, and their main difference is that MP lamps emit a broad spectrum of wavelengths, whereas LP lamps only emit at 253.7 nm (making these lamps less suitable for photolysis, although they are at least as efficient in forming radicals). MP lamps have a very high lamp power (typically from 2,000 W up to 15,000 W). However, the LP lamps have a high energy efficiency (25-30% compared to 15% for MP lamps), and a longer expected life span (9,000-12,000 hours in contrast to 4,000-6,000 hours for MP lamps). On the other hand, because of their higher power fewer MP lamps are required in a reactor compared with LP lamps to achieve an equivalent dose, which results in a smaller footprint of the reactor. The new generation amalgam HO-LP UV lamps (High Output), that has been developed by Philips Lighting, shows an increased output (≥ 230 W), reducing the required footprint of a LP UV/H_2O_2 reactor. In a previous research project [IJpelaar et al., 2010; Hofman-Caris and Beerendonk, 2011a], a comparison of different types of lamps was made. It was found that in general the total conversion in UV/H_2O_2 processes based on LP lamps are comparable to MP based processes, but that the energy requirement of LP processes (Electrical Energy per Order, E_{EO}) is smaller (E_{EO} for LP systems being about half the E_{EO} for MP systems). Besides, the expected lifespan of LP lamps is longer than for MP lamps. This results in lower operating costs for LP based processes. However, these processes will require a larger footprint and thus higher investments costs than MP based processes.

Another important aspect, which has not been addressed yet, it the formation of by-products. Due to their broader emission spectrum, MP lamps are much more efficient for photolysis, but also cause the formation of more by-products (like nitrite in nitrate containing water, but also by-products for example formed by incomplete photolysis of micropollutants or by reaction of Natural Organic Material). Previous research has shown that some of the by-products formed in UV/H_2O_2 processes may cause genotoxicity. In general UV/H_2O_2 processes are followed by filtration over activated carbon, in order to remove the excess H_2O_2. It also has been shown, that this filtration is very effective in removing such byproducts (genotoxic activity has not been shown in water purified by means of UV/H_2O_2 after filtration over active carbon) [Heringa et al., 2011].

9.4 Affinity adsorption

Compared to nanofiltration and UV/H_2O_2 processes, adsorption processes require the smallest amount of operational energy. Adsorption over activated carbon (granular activated carbon (GAC) or powdered activated carbon (PAC)) can be very efficient for removal of, preferably hydrophobic, organic micropollutants. However, for relatively small, hydrophilic or charged molecules, it appears to be less efficient. Besides, competition with e.g. NOM may render the adsorption process less efficient. Affinity adsorption, based on specific interactions with functional groups in the molecule, can be a solution to such problems. It was shown that it can be very effective in adsorbing certain molecular structures, and that competition by e.g. NOM is less a disadvantage than with activated carbon. However, as it is very selective, it probably will not be suitable as a robust removal technique for a broad range of pharmaceuticals, unless it would be possible to use a cascade of adsorbents with different functionalities or a mixture of such adsorbents. Another application of this technology might be as a fine tuning step after nanofiltration or UV/H_2O_2 in order to remove those molecules, which typically are difficult to remove or convert by means of nanofiltration or UV/H_2O_2. Thus energy can be saved in those processes, while still guaranteeing a high removal rate of pharmaceuticals.

At the moment it still is difficult to commercially obtain affinity adsorbents at a large scale and relatively low price. As a result, it also is unknown yet, how such adsorbents can be regenerated on a large scale, and which regeneration frequency would be recommended. In designing a process (partly) based on affinity adsorption, these aspects will have to be taken into account. This still requires some more research.

10 Conclusions

Wastewater treatment processes have not been designed to deal with pharmaceuticals. As a result, many pharmaceuticals and/or their transformation products end up in surface waters. Furthermore, veterinary pharmaceuticals, which are used in large amounts in the Netherlands, may enter the soil environment when manure containing pharmaceuticals is applied on land as fertilizer. As a result, pharmaceuticals and their transformation products can potentially end up in surface waters and groundwater that are used as sources for drinking water. Additionally, it was observed that transformation products that may exhibit comparable pharmacological activity as their parent compounds, are observed in the water cycle as well. So far, based on the results of this screening study, no adverse human health effects of the studied compounds are expected in (sources of) drinking water in the Netherlands. However, the expected increase and changes in pharmaceutical consumption, the presence of pharmaceuticals and transformation products in (surface water) sources for drinking water at concentrations up to µg/L levels and their potential incomplete removal by drinking water treatment techniques suggests that monitoring and risk assessment of both pharmaceuticals and their transformation products remains necessary. Besides, the expected increasing presence of pharmaceuticals in sources for drinking water may eventually result in the need to implement alternative or additional purification techniques in production processes in order to be able to guarantuee safe drinking water in the future.

Both membrane filtration and UV/H_2O_2 can be very efficient processes for removal c.q. conversion of organic micropollutants like pharmaceuticals. Their energy demand is in the same order of magnitude (≤ 1 kWh/m^3). However, for small positively charged and hydrophobic pharmaceuticals (like pindolol, proponolol and phenazone) nanofiltration may not be the most efficient technique, whereas small, hydrophilic ones (like metformine and guanylurea) are difficult to convert using UV/H_2O_2 processes. QSARs can give valuable information on the process efficiency in relation with the molecular structure, although in some cases (like UV photolysis processes) it appears to be difficult to develop reliable QSARs. It was shown, that it is very important that QSARs are validated using external data, in order to obtain an idea about their general applicability.
Which treatment process will be optimum not only depends on its removal c.q. conversion efficiency, but also on site specific conditions (water quality, space available, possibilities to deal with a concentration, regeneration possibilities for adsorbents, etc.) and economic factors.
In general, probably a combination of different techniques will prove to be most efficient. A combination with affinity adsorption may be a very elegant way to deal with pharmaceuticals in the water source, but this still requires some research, as such materials are not yet commercially available at a large scale. Besides, information on regeneration frequency and possibilities also is not available yet. As a result, it is not yet possible to make a fair economic consideration. However, the technological solutions for dealing with pharmaceuticals in (sources of) drinking water are available.

11 Literature

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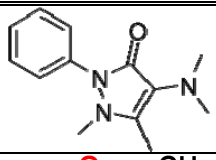
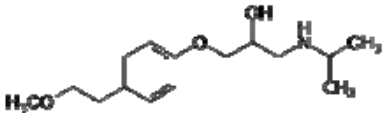
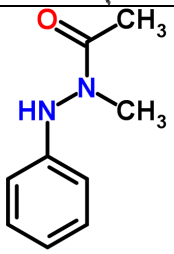
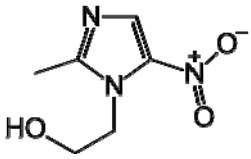
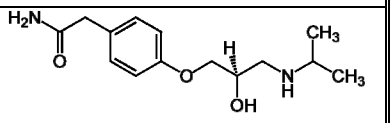
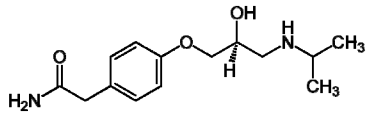
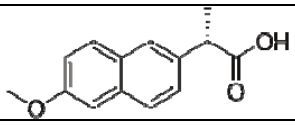
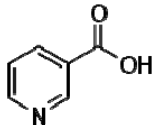
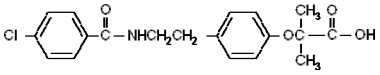
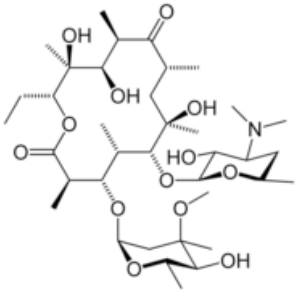
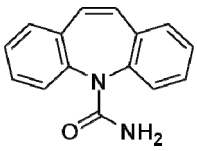
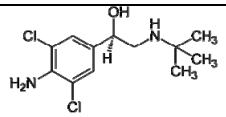
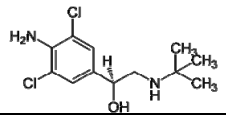
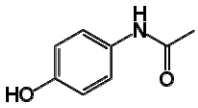
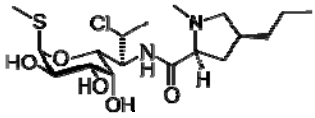
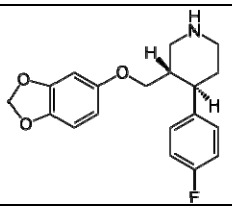
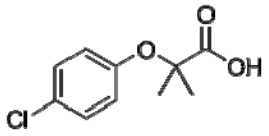
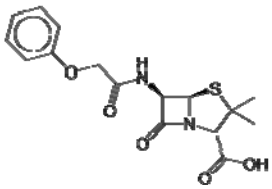
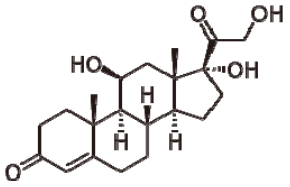
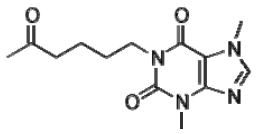
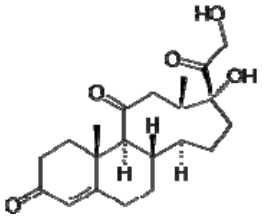
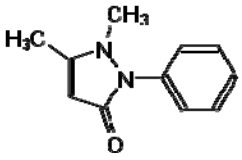
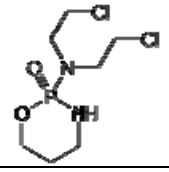
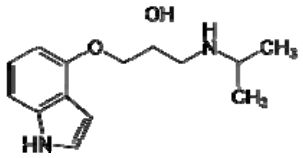
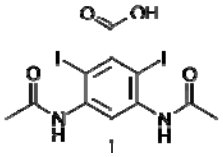
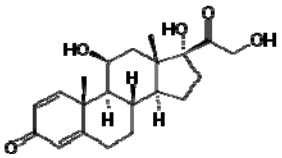
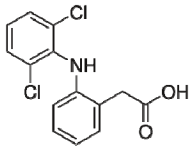
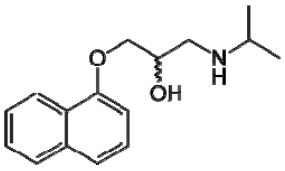
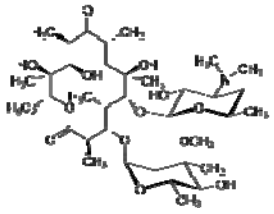
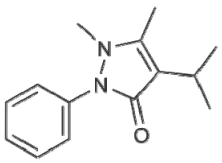
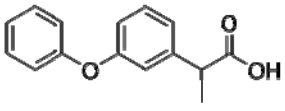
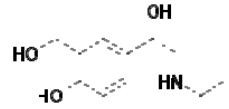
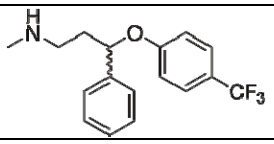
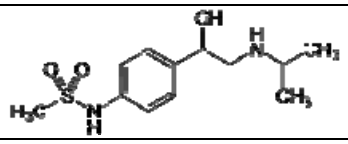
I Selected sets of pharmaceuticals

Table I-1: molecular structure of pharmaceuticals selected for studying removal efficiency means of NF, UV/H2O2 and (affinity) adsorption

Compound	Structure	compound	Structure
Aminopyrine (aminophenazone)		Metoprolol	
AMPH		Metronidazole	
Atenolol	 	Naproxen	
		Niacin	
Bezafibrate		O-desmethyl metoprolol	
Carbamazepine			
Clenbutarol	 	Paracetamol	
Clindamycine		Paroxetine	

Clofibric acid		penicillin V	
Cortisol		Pentoxifylline	
Cortisone		Phenazone	
Cyclophosphamide		Pindolol	
diatrizoic acid		Prednisolone	
Diclofenac		Propranolol	
Erytromycine A		Propyfenazon	
Fenoprofen		Salbutamol	
Fluoxetine		Sotalol	

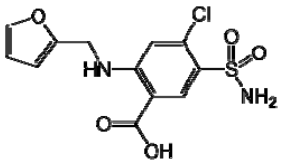
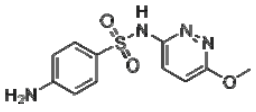
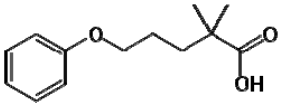
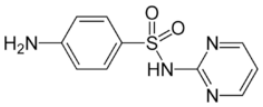
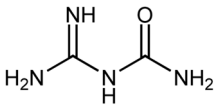
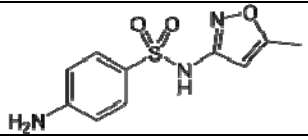
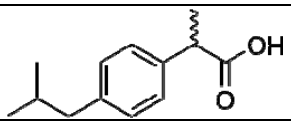
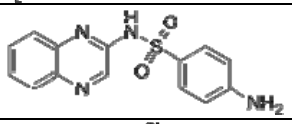
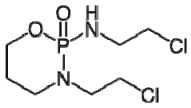
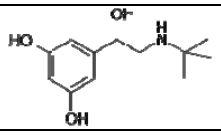
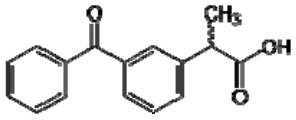
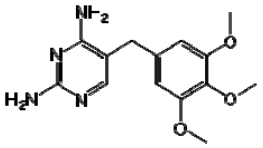
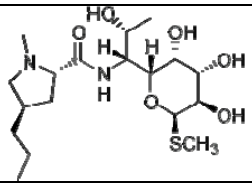
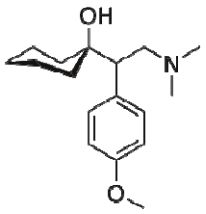
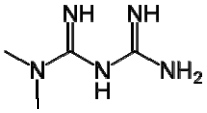
Furosemide		Sulfachloropyridazine	
Gemfibrozil		Sulfadiazine	
Guanylurea		Sulfamethoxazole	
Ibuprofen		Sulfaquinoxaline	
Ifosfamide		Terbutaline	
Ketoprofen		Trimethoprim	
Lincomycine		Venlafaxine	
Metformine			

Table I-2: Properties of compounds selected for NF

Pharmaceutical	MW	log K_{ow}	log $D_{pH\,7.4}$	pK_a	charge @ pH 7
Niacin (vitamine B3, nicotinezuur)	123.1	0.4	-2.9	2.8, 4.2	-1
Metformin	129.1	-1.4	-3.8	12.3	1
Paracetamol (Acetaminophen)	151.1	0.5	0.3	9.4	0
Sulfadiazine	250.1	-0.1	-0.7	2.0, 7.0	-0.5
Fluoxetine metabolite: Norfluoxetine	295.1	4.2	2.7	9.8	1
Paroxetine	329.1	2.6	1.2	9.8	1
Ciprofloxacin	331.3	0.3	-1.4	5.8, 8.7	0
Phenazone	188.1	0.4	0.3	1.4	0
Ibuprofen	206.1	4.0	0.8	4.4	-1
Clofibrate metabolite: Clofibric acid	214.0	2.6	-0.9	3.4	-1
Terbutaline	225.3	0.9	-1.4	8.9	1
Naproxen	230.1	3.2	0.5	4.2	-1
Aminophenazone (aminopyrine)	231.1	1.0	0.8	5	0
Carbamazepine	236.1	2.5	2.7	-	0
Salbutamol	239.3	0.6	-1.9	9.3	1
Fenoprofen	242.3	3.9	0.8	4.2	-1
Pindolol	248.3	2.0	0.1	9.2	1
Gemfibrozil	250.2	4.8	1.8	4.5	-1
Sulfamethoxazole	253.1	0.9	-0.2	1.8, 5.6	-1
Ketoprofen	254.3	3.1	-0.3	4.3	-1
Propranolol	259.3	3.5	1.3	9.6	1
Cyclophosphamide	260.0	0.6	0.2	0, 12.8	0
Atenolol	266.2	0.2	-1.7	9.4	1
Metoprolol	267.2	1.9	-0.1	9.5	1
Sotalol	272.1	0.2	-1.6	9	1
Clenbuterol	277.2	2.0	1.0	1.4, 9.6	1
Pentoxifylline	278.3	0.3	0.3	0.3	0
Trimethoprim	290.1	0.9	0.6	7.2	0.5
Diclofenac	295.0	4.5	1.0	4.2	-1
Bezafibrate	361.8	4.3	0.7	3.4	-1

Data from [1-3], chemspider and marvin.

Table I-3: Properties of compounds selected for UV/H_2O_2

Compound	MW (Da)	Quantum yield* molar adsorption (mol L^{-1} cm^{-1})	OH reaction rate (mol L-1 s^{-1})
Carbamazepine	236	4	7.33E+09
Metoprolol	267	28	7.60E+09
Ibuprofen	206	49	6.89E+09
Naproxen	230	119	8.87E+09
Clofibrate metabolite: Clofibric acid	214	255	5.04E+09
Sulfamethoxazole	253	553	5.50E+09
Phenazone	188	563	8.43E+09
Diclofenac	295	1483	7.50E+09
Ketoprofen	254	3065	6.89E+09
Aminophenazone (aminopyrine)	231		2.50E+10
Atenolol	266		7.67E+09
Bezafibrate	361		7.70E+09
Clenbuterol	277		
Cyclophosphamide	260		
Fluoxetine metabolite: Norfluoxetine	295		
Gemfibrozil	250		1.00E+10
Metformin	129		
Niacin (vitamine B3, nicotinezuur)	123		2.60E+08
Paracetamol (Acetaminophen)	151		6.00E+09
Paroxetine	329		
Pentoxifylline	278		7.70E+09
Pindolol	248		
Propranolol	259		1.04E+10
Sotalol	272		
Sulfadiazine	250		
Terbutaline	225		
Trimethoprim	290		6.90E+09
Metronidazole	171	7	4.80E+09
Doxycycline	444	138	1.50E+09
Diatrizoic acid	614	1092	5.40E+08
Cortisol	362		
Cortisone	360		
Prednisolone	360		
Ciprofloxacin	331	128	5.16E+09
Fenoprofen	242		
Salbutamol	239		

The sensitivity to photolysis is indicated by the quantum yield multiplied by the molar adsorption and the sensitivity to oxidation is indicated by the OH radical reaction rate (not sensitive, little sensitive, sensitive). For some compounds, these sensitivities are unknown but estimations could be made from reported removal data.

Table I-4: Properties of compounds selected for affinity adsorption

compound	MW	Log K_{ow}	pKa	log $D_{pH7.4}$	charge @ pH 7	COOH	OH	NH/NH_2	phenyl
metformin	129	-2.64	12.3	-3.8	1			x	
paracetamol	151	0.46	9.38	0.3	0		x	x	x
ibuprofen	206	3.97	4.4	0.8	-1	x			x
Clofibric acid	214	2.57	3.4	-0.9	-1	x			x
naproxen	230	3.18	4.15	0.47	-1	x			x
carbamazepine	236	2.45		2.67	0			x	x
salbutamol	239	0.64	9.3	-1.9	1		x	x	x
sulfadiazine	250	-0.09	2.0, 7.0	-0.7	-0.5			x	x
pindolol	248	2	9.2	0.1	1		x	x	x
gemfibrozil	250	4.77	4.5	1.8	-1	x			x
sulfamethoxazole	253	1.28	1.8, 5.6	-0.2	-1			x	x
cyclophosphamide	260	0.63	0, 12.8	0.2	0				
atenolol	266	0.16	9.6	-1.7	1			x	x
sotalol	272	0.24	9	-1.6	1			x	x
pentoxfilline	278	0.29	0.3	0.3	0				x
oxazepam	287	2.24	11.6	2.3	0		x		x
trimethoprim	290	0.91	7.2	0.6	0.5			x	x
diclofenac	296	4.51	4.15	1	-1	x		x	x
temazepam	301	2.19	10.7	2.2	0		x		x
metamizole	310	-4.76		-4.1	-1			x	x
paroxetine	329	3.95	9.77	1.19	1			x	x
ciprofloxacin	331	0.28	5.8, 8.7	-1.4		x		x	x
prednisolon	360	1.62	13.86	1.49	0	x	x		x
cortisone	360	1.47	13.88		0	x	x		
cortisol	362	1.61	13.87	1.43	0	x	x		
bezafibraat	364	4.25	3.4	0.7	-1	x		x	x
amoxilline	365	0.85	3.23	-2.73	-1	x	x	x	x
doxycycline	444	-0.22		-5	0		x	x	x
verapamil	455	3.79	9.68	2.33	1			x	x
Diatrizoic acid	614	1.37	2.17	-2.7	-1	x		x	x
erythromycin	733	3.06		2.08	0		x		

Table I-5: Additional pharmaceuticals selected for adsorption studies: derivatives and metabolites.

compound	MW	Log K_{ow}	pKa	log $D_{pH7.4}$	charge @ pH 7	COOH	OH	NH/NH_2	phenyl
salicylzuur	138	2.26	2.8, 13.3	-1.1	-1	x	x		x
Acetyl salicylzuur	180	1.19	3.49	-1.9	-1	x			x
phenazone	188	0.38	1.4	0.3	0				x
propyphenazone	230	1.94	-0.24	1.74	0				x
aminophenazone	231	1	3.46	0.76	0			x	x
Hydroxy ibuprofen	222	2.29	4.6	-1.2	-1	x	x		x
metoprolol	267		9.5	-0.1	1		x	x	x
4-(2-hydroxy-3-isopropylamino-propoxy) phenylacetic acid	267		3.54	-1.35	-1	x	x	x	x
O-desmethyl-metoprolol	253	1.28	9.7	-0.8	1		x	x	x

II Analytical data for pharmaceuticals and their metabolites

Table II-1: Reproducibility (RP), limit of detection (LD) and reporting limit (RL) of pharmaceuticals and metabolites in drinking water based on standards in MilliQ water

Components	RP (n=8) 0.05 µg/l (%)	RP (n=8) 0.5 µg/l (%)	LD calculated (3 x S) µg/l	RL determined µg/l	Recovery at RL level (%)	RP at RL revel (%)
2-Hydroxy carbamazepine	3.5	1.1	0.002	0.01	104.0	10.0
3-Hydroxy carbamazepine	2.0	2.3	0.001	0.01	92.6	4.5
4-Acetaminophen Sulphate	5.0	2.4	0.004	0.025	66.2	10.9
4-formylaminoantipyrine	3.5	1.4	0.001	0.01	111.9	3.8
10.11-trans diol carbamazepine	3.2	1.6	0.001	0.01	101.5	2.9
α-Hydroxy metoprolol	3.0	3.0	0.001	0.01	109.1	4.4
Acetyl sulfadiazine	4.6	3.5	0.001	0.01	93.0	3.4
AMPH	4.9	1.7	0.003	0.01	92.0	10.4
Anhydro erythromycin A	17.1	7.1	0.005	0.05	36.8	17.1
Atenolol	2.0	2.7	0.001	0.01	96.5	4.7
Bezafibrate	2.0	1.2	0.001	0.01	90.7	2.5
Carbamazepine	1.1	0.9	0.001	0.01	94.6	1.2
Carbamazepine-10.11-epoxide	1.9	1.7	0.002	0.01	108.2	6.5
Ciprofloxacin	77.2	2.5	0.13	0.5	314.8	2.5
Clenbuterol	4.2	1.7	0.002	0.01	99.1	6.1
Clindamycin	4.1	3.9	0.003	0.01	108.4	11.4
Clofibric acid	7.7	2.9	0.002	0.01	76.1	9.0
Cortisol	5.6	3.6	0.006	0.025	80.9	10.5
Cortisone	7.8	2.9	0.009	0.025	92.9	12.1
Cyclophosphamide	4.6	3.1	0.003	0.01	99.2	10.3
Diatrizoic acid	14.2	5.8	0.003	0.01	52.8	18.8
Diclofenac	0.7	1.5	0.001	0.01	96.9	2.6
Dimethylaminophenazone	3.2	1.4	0.003	0.01	102.0	4.0
Erythromycin A	25.6	6.5	0.005	0.025	46.2	15.7
Fluoxetine	8.9	3.0	0.001	0.01	89.9	5.9
Furosemide	4.9	6.2	0.003	0.01	105.9	9.5
Gemfibrozil	2.5	2.0	0.002	0.01	97.9	7.0
Guanylurea *	n.b.	3.7	0.03	0.5	55.2	3.7
Hydroxy ibuprofen	53.1	5.3	0.06	0.5	105.4	5.3
Ifosfamide	6.6	1.4	0.002	0.01	103.6	7.0
Ketoprofen	0.9	1.2	0.002	0.01	99.7	4.6
Lincomycin	4.3	2.0	0.003	0.01	110.6	9.7
Metformine *	2.6	4.2	0.003	0.05	98.5	2.6
Metoprolol	2.7	2.8	0.002	0.01	134.8	4.9
Metronidazole	1.0	2.0	0.001	0.01	96.3	3.0
N4-acetyl Sulfamethoxazole	5.7	1.9	0.002	0.01	103.2	6.7
Naproxen	6.5	3.7	0.003	0.01	73.5	14.7
Niacin	2.9	2.2	0.001	0.01	104.2	4.2
Norfluoxetine	63.2	7.7	0.3	0.5	256.7	7.7

Components	RP (n=8) 0.05 µg/l (%)	RP (n=8) 0.5 µg/l (%)	LD calculated (3 x S) µg/l	RL determined µg/l	Recovery at RL level (%)	RP at RL revel (%)
O-Desmethylmetoprolol	10.4	14.0	0.004	0.01	108.4	11.5
O-Desmethyl Naproxen	11.8	3.1	0.02	0.05	85.9	11.8
O-Desmethyltramadol	2.4	2.0	0.001	0.01	111.4	3.4
Oxcarbamazepine	1.7	3.4	0.003	0.01	81.1	9.4
Paracetamol (Acetaminophen)	2.7	1.1	0.002	0.01	93.6	5.2
Paroxetine	21.5	7.5	0.06	0.05	203.0	21.5
Penicillin V	12.2	5.1	0.003	0.01	65.7	17.1
Pentoxifylline	2.6	2.7	0.001	0.01	97.9	4.0
Phenazone	4.8	2.0	0.002	0.01	103.6	5.1
Pindolol	3.4	0.8	0.001	0.01	111.1	3.3
Prednisolone	9.2	3.2	0.01	0.05	89.9	9.2
Propranolol	2.6	2.9	0.002	0.01	107.0	4.8
Propyphenazone	2.7	1.1	0.001	0.01	104.0	3.4
Salbutamol	2.3	2.2	0.001	0.01	86.6	5.7
Salicylic acid	116.1	146.4	0.6	5.0	79.2	5.0
Sotalol	2.0	2.6	0.001	0.01	105.9	4.6
Sulfachloropyridazine	4.2	1.8	0.002	0.01	91.6	7.2
Sulfadiazine	2.2	0.9	0.001	0.01	110.3	3.0
Sulfamethoxazole	3.4	1.6	0.002	0.01	98.2	8.2
Sulfaquinoxalin	3.1	1.5	0.002	0.01	102.1	7.2
Terbutaline	6.7	5.5	0.002	0.01	73.2	10.2
Tramadol	2.8	2.2	0.001	0.01	115.0	2.1
Trimethoprim	2.7	2.6	0.002	0.01	109.0	5.9
Venlafaxine	5.7	3.3	0.002	0.01	113.6	7.1
Oxytetracycline				0.1		
Tetracycline				0.1		
Sulfaclozine				0.05		
Tylosin				0.05		
doxycycline				0.1		

* Analysis by means of Luna HILIC column

** EDTA was added to the sample to reduce the amount of free bivalent cations that can form complexes with these compounds and hamper analysis.

III Occurrence of pharmaceuticals and their transformation products in the environment

Table III-1: List of analyzed and detected chemicals and their maximum concentrations

Pharmaceutical/ X-ray contrast medium	consumption	Load	Excretion by humans	Removal by wastewater treatment plant	Residue found	Residue predicted
	kg/year	kg/y	% of total	% of total	% of consumption	% of consumption
Roxithromycine	3665	1073	60	37	29.3	37.7
Clarithromycine	7784	1055	18	45	13.6	10.0
Clindamycine	5660	1380	19	?	24.4	19.0
Erythromycine	10677	2191	98	67	20.5	32.0
Sulfamethoxazole	26713	2491	20	59	9.3	8.1
Trimethoprim	6040	502	45	16	8.3	37.6
Atenolol	9501	1299	83	8	13.7	76.7
Metoprolol	32354	2132	11	10	6.6	9.9
Sotalol	12132	3538	100	11	29.2	94.3
Pentoxyfylline	50930	3906	7	?	7.7	7.0
Bezafibrate	19842	2877	51	68	14.5	16.4
Carbamazepine	43761	6184	26	9	14.1	23.7
Ibuprofen	131592	1512	30	74	1.1	7.7
Diclofenac	41354	4102	16	32	9.9	10.9
Ioxitalaminic acid	7819	7819	>95	0	20	95.0
Iorpomide	36416	36416	>92	61	38.5	35.9
Iohexol	9764	9764	100	?	60.8	100.0
Iomeprol	24180	24180	100	9	50.5	91.0
Iopamidol	21181	21181	90	0	70.4	90.0
Amidotrizoinic acid	25608	25608	>95	8	50.3	87.4

Table III-2: Pharmaceutical sales in the Rhine catchment area and calculated and predicted loads of pharmaceuticals in the Rhine

	Q_{cons-G} (kg/y)	Q_{cons-S} (kg/y)	Q_{cons-F} (kg/y)	Q_{cons}, (kg/y) [g]	Q_{Rhine} at Lobith, (kg/y)	$Q_{Rhin-pred}$ at Lobith, (kg/y)
Inhabitants per country *10⁶	**82.4**	**7.3**	**58.5**			
Inhabitants Rhine catchment area per country *10⁶ (ICPR, 2005)	**36.7**	**5.0**	**3.7**	**45.6** (upstream of Lobith)		
Antibiotics						
Roxithromycin	7359 [a]	149 [b]	4182 [f]	3665	1073	1380
Clarithromycin	12360 [a]	1700 [c]	16889 [f]	7784	1055	777
Clindamycin	11446 [a]	*1014* [e]	1236 [f]	5660	1380	1075
Anhydro-erythromycin-A	19958 [a]	*1768* [e]	10294 [f]	10677	2191	3420
Sulfamethoxazole	53600 [a]	2300 [c]	17519 [f]	26713	2491	2175
Trimethoprim	12183 [a]	520 [c]	20603 [f]	6040	502	2271
Beta Blockers						
Atenolol	13551 [a]	3071[c]	10596 [f]	9501	1299	7287
Metoprolol	64699 [a]	*3807* [e]	12602 [f]	32354	2132	3199
Sotalol	23945 [a]	877 [c]	24808 [f]	12132	3538	11445
Lipid regulators						
Pentoxifylline	100180 [a]	*8875* [e]	19103 [f]	50930	3906	3565
Bezafibrate	39158 [a]	1574 [b]	3508 [f]	19842	2877	3247
Anti epilepticum						
Carbamazepine	83299 [a]	6260 [b, h]	33364 [f]	43761	6184	10378
Analgesics / Anti inflammatory						
Ibuprofen	250792 [a]	22471 [b, h]	58353 [f]	131592	1512	10177
Diclofenac	78579 [a]	6819 [b, h]	22640 [f]	41354	4102	4489
X-ray contrast medium						
Ioxitalamic acid	8895 [a]	6819 [d]	20884 [f]	7819	1565	7428
Iopromide	97817 [a]	8965 [b, d]	12810 [f]	36416	14024	13066
Iohexol	8053 [a]	4614 [d]	46774 [f]	9764	5938	9764
Iomeprol	44727 [a]	1650 [d]	47355 [f]	24180	12210	22004
Iopamidol	38165 [a]	2739 [d]	34540 [f]	21181	14922	19063
Amidotrizoinic acid	50226 [a1]	*4450* [e]	13179 [f]	25608	12874	22381

a) Average German sales of pharmacies and hospitals from 1996, 1998 and 2001 (Rohweder, 2003). **b)** Average Swiss sales of pharmacies in 2000 (Thomas and Joss, 2006). **c)** Average Swiss sales in 2000 and 2004 covering all relevant (human) distribution channels (Ort et al., 2009), **d)** Average Swiss sales in hospitals in 2004 (Weissbrodt et al., 2009). **e)** No data available, consumption assumed to be the same as other countries in the Rhine catchment area. **f)** Average French sales of pharmacies and hospitals in 2002-2008 (Personal communication P. Cavalié 2009, AFSSAPS). **g)** Calculated upstream of Lobith under the assumption that consumption of pharmaceuticals is homogenously spread over the inhabitants of different regions within a country. **h)** Total consumption includes sales at public pharmacies, hospitals, drug stores and self dispensing physicians, which was estimated according to (McArdell et al., 2009), 65% of carbamazepine, 70% of ibuprofen and 57% of diclofenac is sold via public pharmacies in Switzerland.

IV Occurrence of veterinary pharmaceuticals and their transformation products in the environment

Table IV-1: Veterinary pharmaceuticals, consumption and occurrence in the environment

Pharmaceutical	Human consumption	Cons vet (kg/y NL)[9]	Occurence in surface water and STP	Occurence in groundwater	Occurence in soil and sediment
Amoxicillin	yes	1187.45	Yes		
Dimetridazole			Yes		
Doxycycline	yes	190906			
Erythromycin A / Erythromycin h2o	yes		Yes		
Ivermectin (dihydroavermectin)					
Lincomycin	yes	424.9	Yes	Yes	Yes
Mebendazole			Yes		
Oxytetracycline	yes	299298	Yes		Yes
Penicillin V = Phenoxymethylpenicillin	yes	96063			
Sulfachloropyridazine = Sulfaclozine	yes	37			
Sulfadiazine		92611	Yes		Yes
Sulfamethoxazole	yes		Yes	Yes	
Sulfaquinoxalin		52536			
Tetracycline	yes	30			Yes
Trimethoprim	yes		Yes		
Tylosin / Tilmicosin		145870	Yes		
17-alpha-Ethinylestradiol-3-methylether = mestranol	yes				
Ampicillin	yes	9893			
Ampicilloic acid	yes				
Cloxacillin	yes	2671			
Colistin		4442			
Enrofloxacin		6906	Yes		
Florfenicol		2483			
Flumequine		9106	Yes		
Ketamine	yes		Yes		
Lincomycin	yes	7992			
Neomycin		7992			
Penicillin G = Benzylpenicillin		7787			
Penicilloic acid (amoxicilloic acid?)	yes				
Sulfadoxin		2764			
Timilcosin		8446			
Chlorotetracycline					

VPs are sometimes applied as mixture. The ratio in which the mixture is applied is not given. Therefore the listed consumption might deviate slightly from actual consumption.

V Experiments with nanofiltration

A pilot plant consisting of two parallel membrane pressure vessels, each accommodating a single 2521 nanofiltration spiral wound membrane element was employed to perform membrane filtration experiments, see Figure II-1 . Pre-filtered tap water (1 µm cartridge filters) from Nieuwegein, the Netherlands, was used as feed water. The experiments were carried out at a constant cross-flow velocity of 0.1 m/s and a feed flow of 350 L/h per pressure vessel, corresponding to practical conditions of full-scale membrane elements. Concentrate needle valves were used to set and maintain 10% recovery (corresponding to 35 L/h of permeate) during the test.
One of the two elements was subjected to biofouling by dosing of an easily degradable carbon source (Na-acetate). The filtration protocol applied is schematically depicted in Figure II-2.

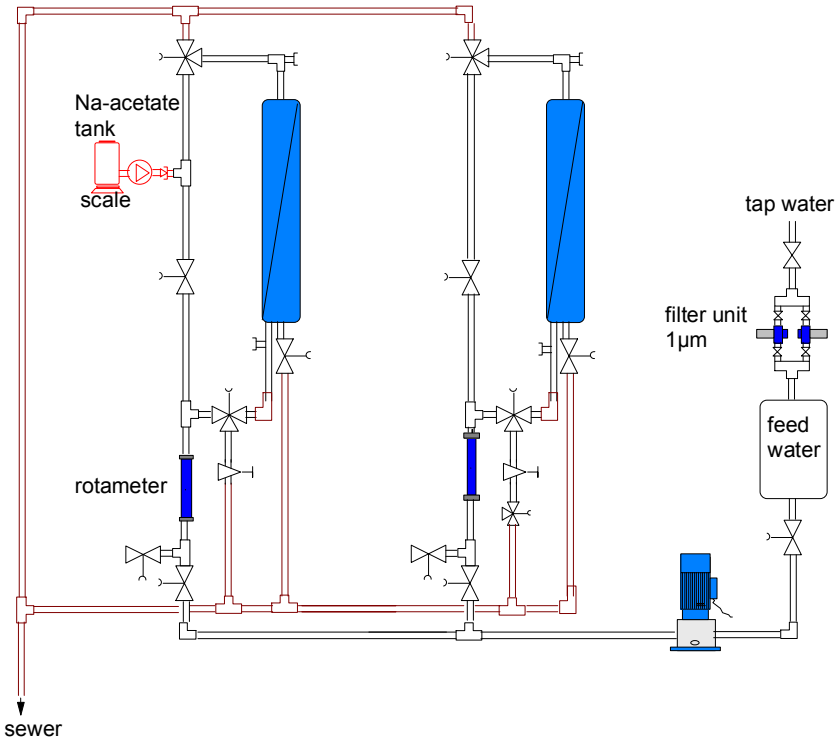


Figure V-1: Schematic diagram of the pilot installation employed for filtration experiments

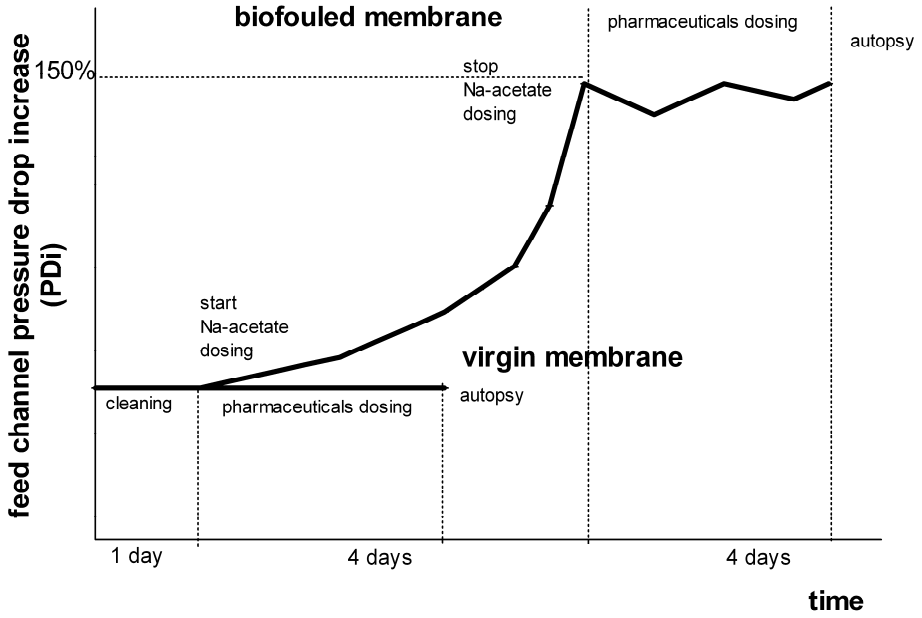


Figure V-2: Schematic illustration of the filtration protocol applied for virgin and biofouled membranes

The membranes used in this study were commercially available Desal HL 2521 thin film composite modules with a cross linked aromatic polyamide top layer. According to the membrane manufacturer, the membranes have a molecular weight cut off (MWCO) of 150-300 g/mol.
Surface properties of virgin and biofouled membranes were determined and compared in order to evaluate whether the presence of biofilm alters the surface characteristics, namely pore size, surface charge, surface energy and hydrophobicity which are the governing parameters in solutes rejection.

Table V-1: Surface properties of clean and biofouled NF membranes

	predicted membrane pore size (nm)	surface charge (mV)	surface energy (mJ/m²)				ΔG_{MLM} hydrophilicity (mJ/m²)	ATP (ng/cm²)
				apolar	polar			
			γ^{TOT}	γ^{LW}	γ^{+}	γ^{-}		
virgin	0.6	-33±7	**56.7**	23.9	5.4	49.2	21.3	
biofouled	0.5	-35±7	**54.3**	19.5	5.3	57.6	27.9	2.9

It was found that biomass attachment did not significantly modify surface charge and pore size. Biomass accumulation on the membrane surface was monitored by ATP measurements, which revealed that 2.5, 1.0 and 3.4 ± 0.1 ng ATP/cm² accumulated at the feed side, in the middle and at the brine side of the module, respectively.
It was observed that positively charged pharmaceuticals display only slightly lower rejections than the negatively charged and neutral organic solutes, likely as a consequence of electrostatic repulsion with the negatively charged membrane surface [Nghiem et al., 2005; Xu et al., 2006; Verliefde et al., 2007 and 2008] (Figure II-3A).

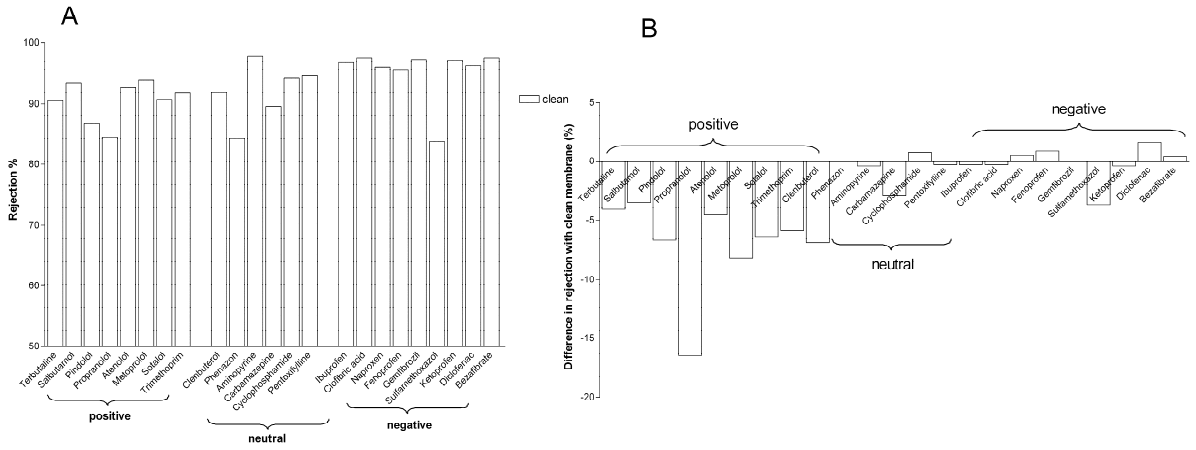


Figure V-3:: (A) Rejection by a clean membrane and (B) absolute difference in rejection between virgin and biofouled membranes

The difference in behavior of differently charged compounds becomes more clear with biofouled membranes. In this case a significant decrease in the removal of positively charged pharmaceuticals was observed, whereas the removal of neutral or negatively charged compounds was hardly affected. This probably can be attributed to the presence of negatively charged biomass at the membrane surface.

Surface tension data were used to determine the free energy of interaction between solute and membranes (ΔG), according to equation V-4.

$$\Delta G_{MLM} = -2\left(\sqrt{\gamma_M^{LW}} - \sqrt{\gamma_L^{LW}}\right)^2 - 4\left(\sqrt{\gamma_M^+\gamma_M^-} + \sqrt{\gamma_L^-\gamma_L^+} - \sqrt{\gamma_M^-\gamma_L^+} - \sqrt{\gamma_L^-\gamma_M^+}\right) \qquad \text{(V-4)}$$

In which γ_L represents the surface tension of the liquid and γ_M of the solid (pharmaceutical) surface [van Oss, 2006].

ΔG represents the amount of energy required or obtained from the interaction between the pharmaceuticals and the membrane surface immersed in water. If $\Delta G > 0$ repulsion occurs, if $\Delta G < 0$ attraction will be observed. Results obtained for 14 pharmaceuticals are shown in Table II-2.

Table V-2: Surface tension (γ) components of a selection of pharmaceuticals and interaction energy of these solutes with virgin and biofouled membranes. All values are expressed as mJ/m².

Surface energy / pharmaceuticals	γ_{Tot}	ΔG_{virgin}	$\Delta G_{biofouled}$
Terbutaline	58.6	5.6	6.7
Propranolol	48.6	6.8	4.6
Atenolol	25.8	5.4	6.7
Metoprolol	44.7	10.5	6.7
Sotalol	42.9	7.8	9.2
Trimethoprim	43.5	7.5	9.1
Aminopyrine	48.3	7.8	9.2
Carbamazepine	46.5	5.4	6.6
Pentoxifylline	45.2	8.0	9.5
Ibuprofen	37.9	0.7	1.7
Clofibric acid	45.4	5.2	6.3
Naproxen	43.1	1.9	3.0
Gemfibrozil	39.1	1.0	2.1
Diclofenac	39.3	9.2	10.9

Relating the data in Table III-2 to the rejection of the compounds results in Figure II-4.

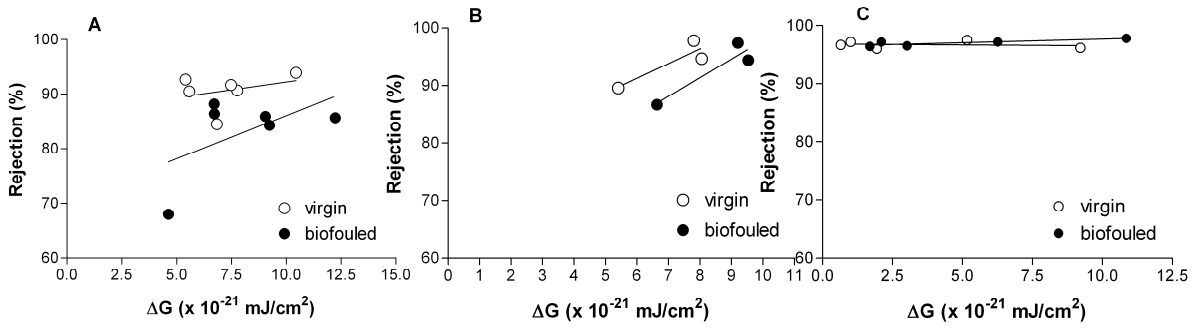


Figure V-4: Rejection of (A) positively charged, (B) neutral and (C) negatively charged solute by biofouled membrane as a function of interaction energy between solutes and virgin (ΔGvirgin) and biofouled (ΔGbiofouled) membranes. Lines indicate the linear regression

From Figure III-4 it was concluded, that in general higher values for ΔG result in a less spontaneous transfer of the solute through the membrane, thus resulting in a higher rejection. For neutral solutes removal is predominantly controlled by solute-membrane hydrophobic affinity. For negatively charged solutes, the rejection seems to be largely independent of ΔG, due to prevailing electrostatic repulsion.

VI UV/H_2O_2 pilot reactor

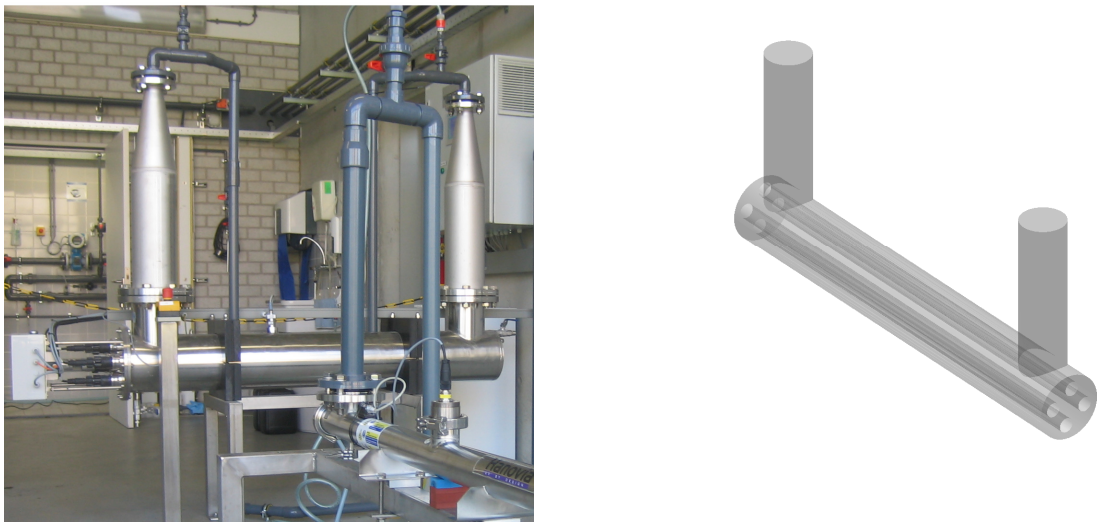


Figure VIV-1: LP pilot reactor at Dunea; on the left side the actual reactor, on the right side the schematic view

Table VI-1: Characteristics of pretreated Dunea water

Temperature (˚C)	pH	UV-T (%)	NO_3^- (mg N/L)	HCO_3^- (mg/L)	NPOC (mg/L)
6.7	7.8	74.1	3	181	5

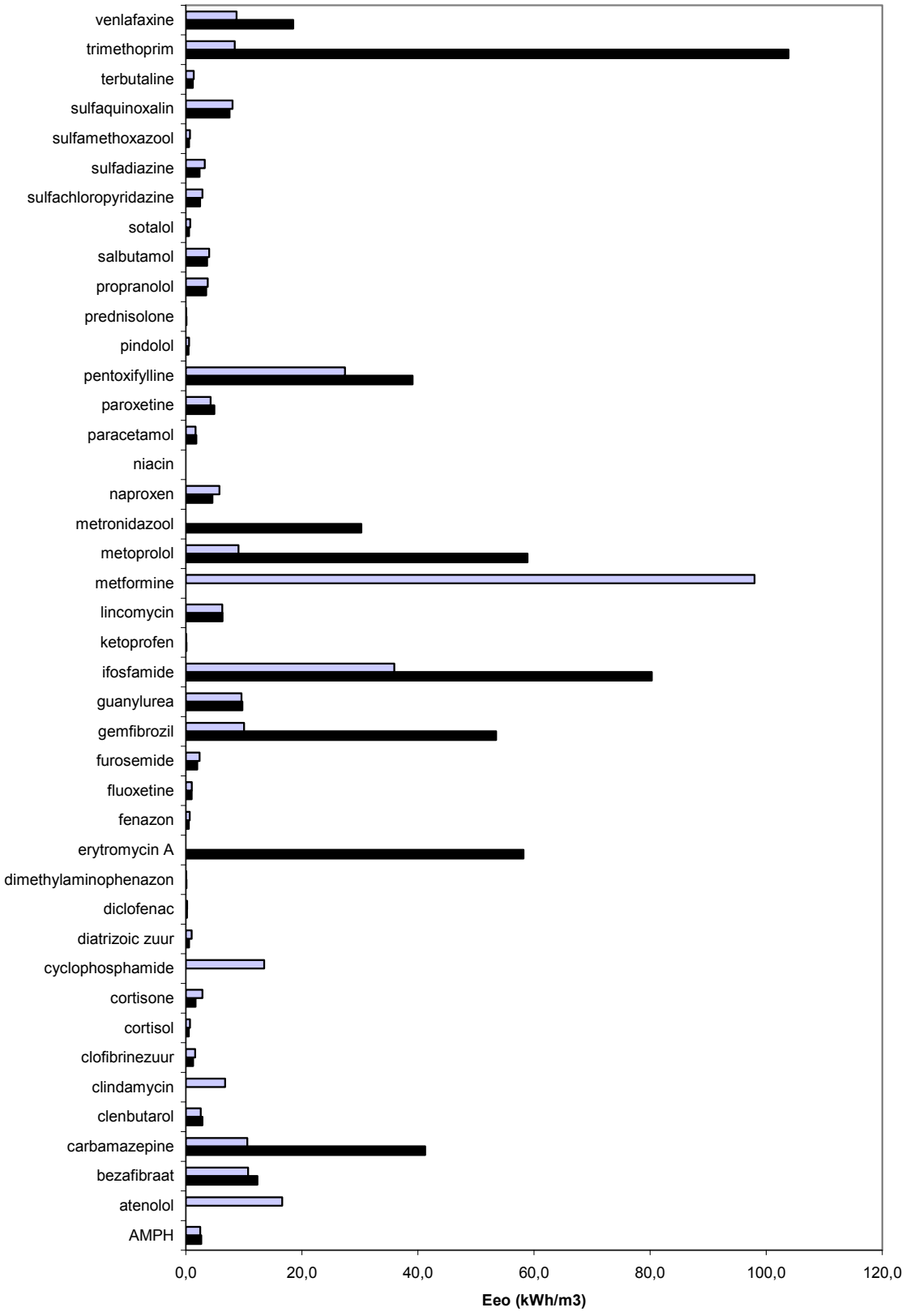


Figure VI-2: E_{EO} values for the photolysis process. Grey: power ballast setting 60%; black: power ballast setting 100%

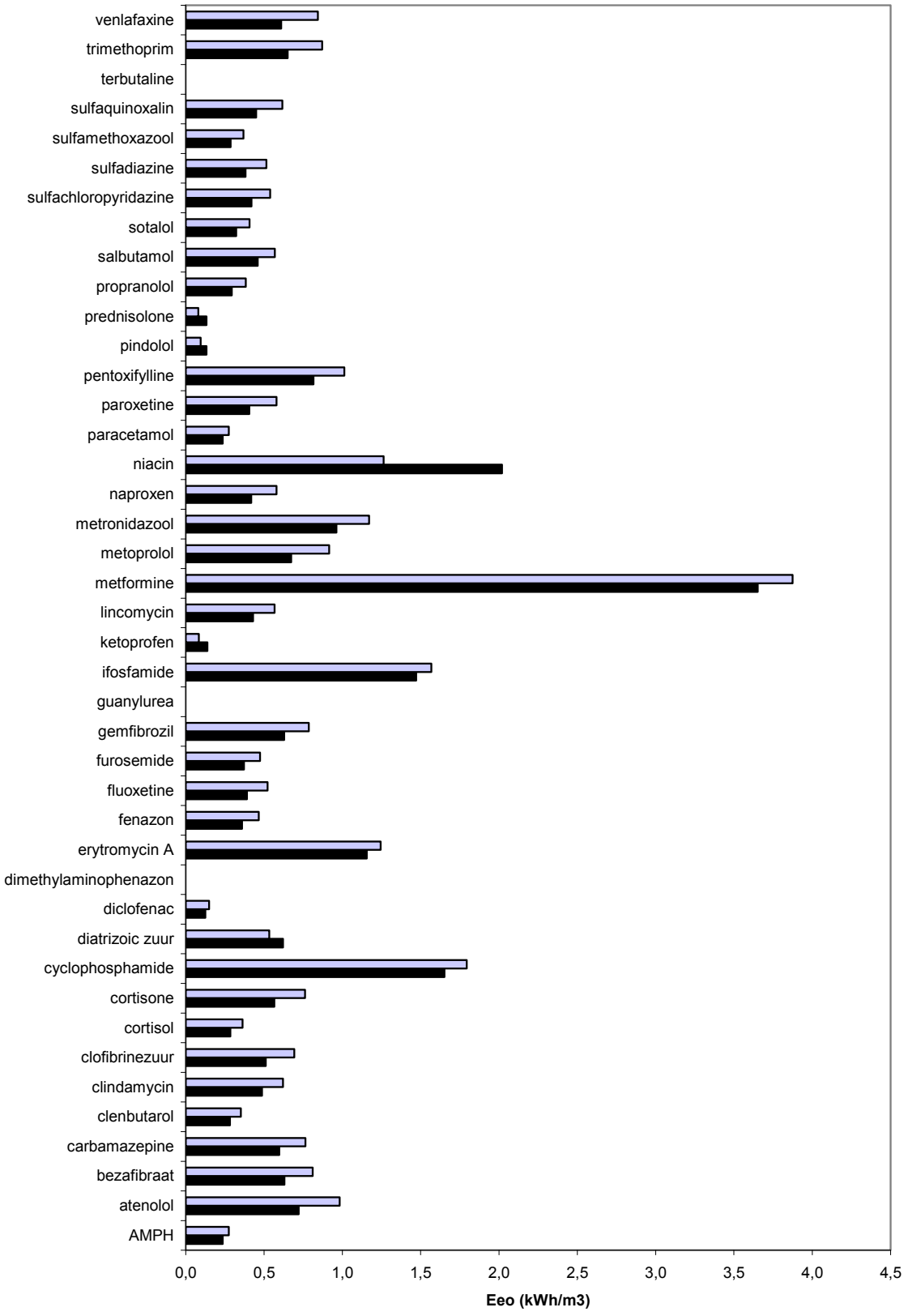


Figure VI-3: E_{EO} values for the combined photolysis and oxidation process. Grey: power ballast setting 60%; black: power ballast setting 100%.

VII Removal by means of adsorption

Table VII-1: average composition of Nieuwegein drinking water

parameter	Nieuwegein drinking water
UV-T	87%
HCO_3^-	247-268
NO_3^-	<1 – 1,4
TOC	1,6-1,9
pH	8

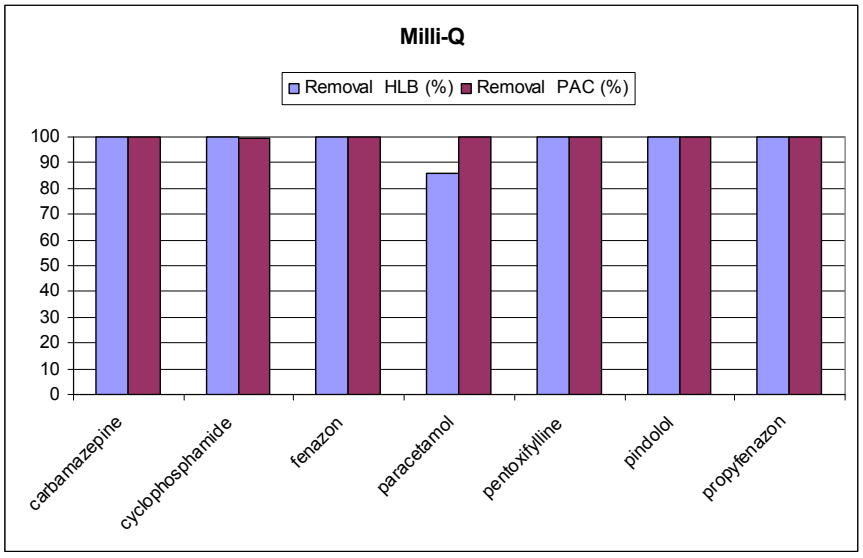


Figure VII-1: adsorption of selected pharmaceuticals in MilliQ on Oasis HLB

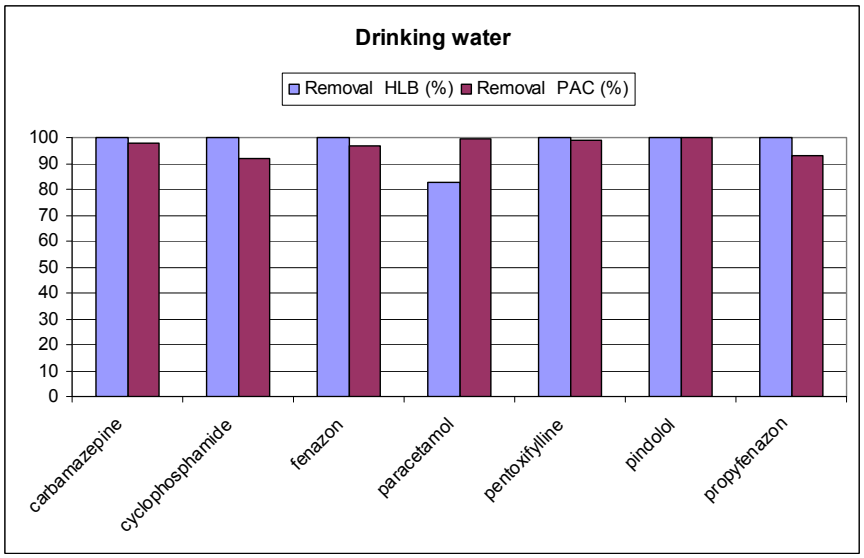


Figure VII-2: adsorption of selected pharmaceuticals in Nieuwegein drinking water on Oasis HLB

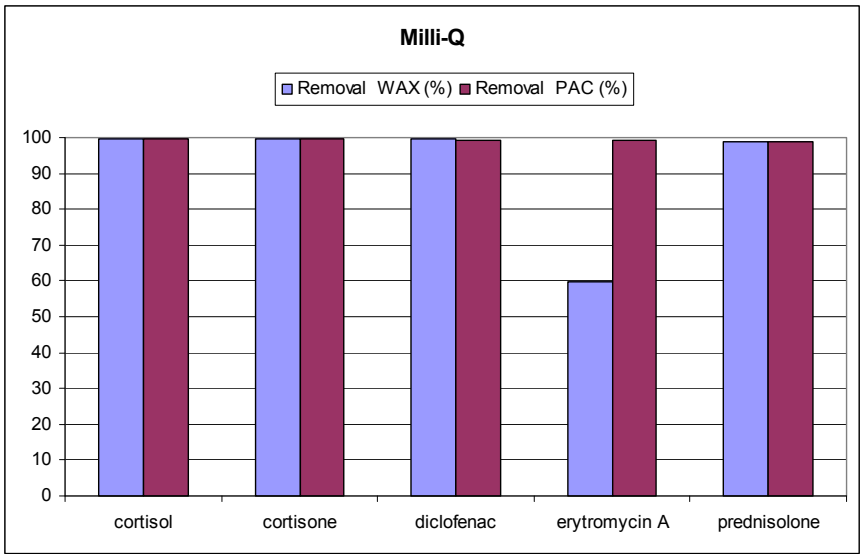


Figure VII-3: adsorption of selected pharmaceuticals in MilliQ on Oasis WAX

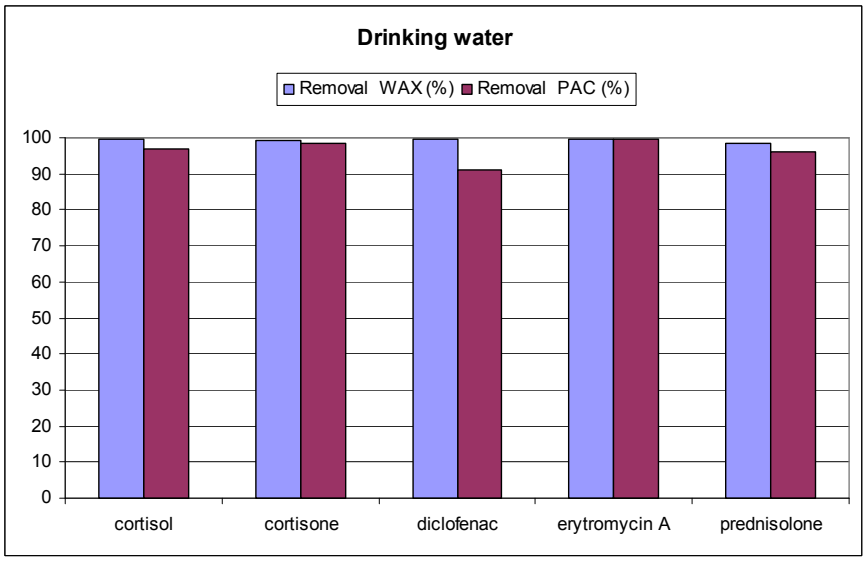


Figure VII-4: adsorption of selected pharmaceuticals in Nieuwegein drinking water on Oasis WAX

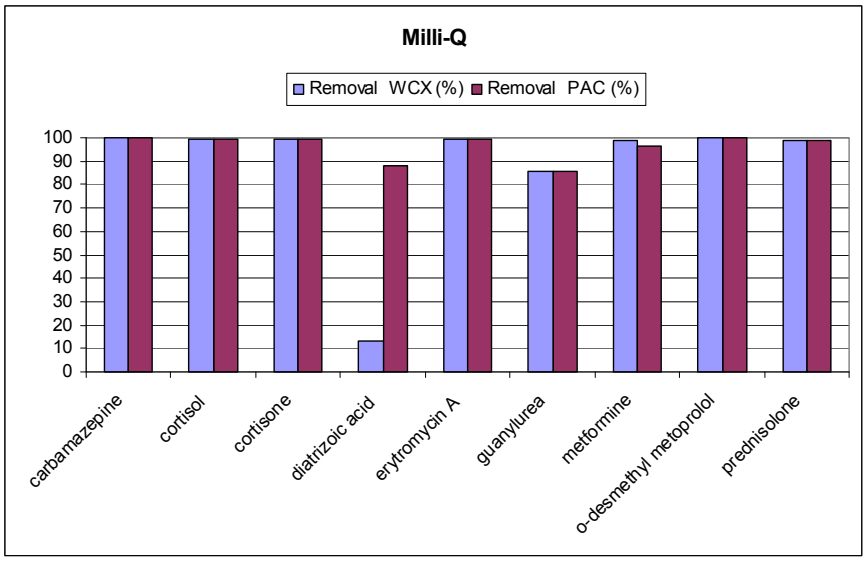


Figure VII-5: adsorption of selected pharmaceuticals in MilliQ on Oasis WCX

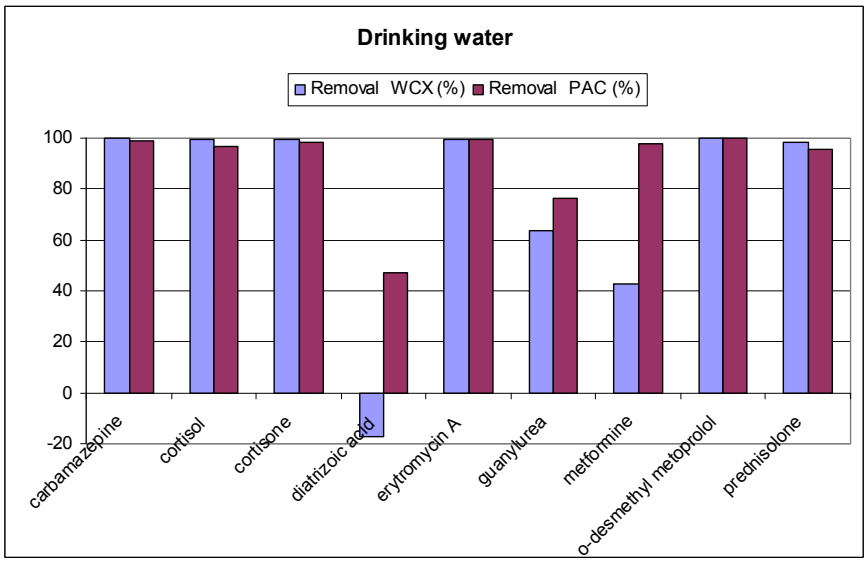


Figure VII-6: adsorption of selected pharmaceuticals in Nieuwegein drinking water on Oasis WCX

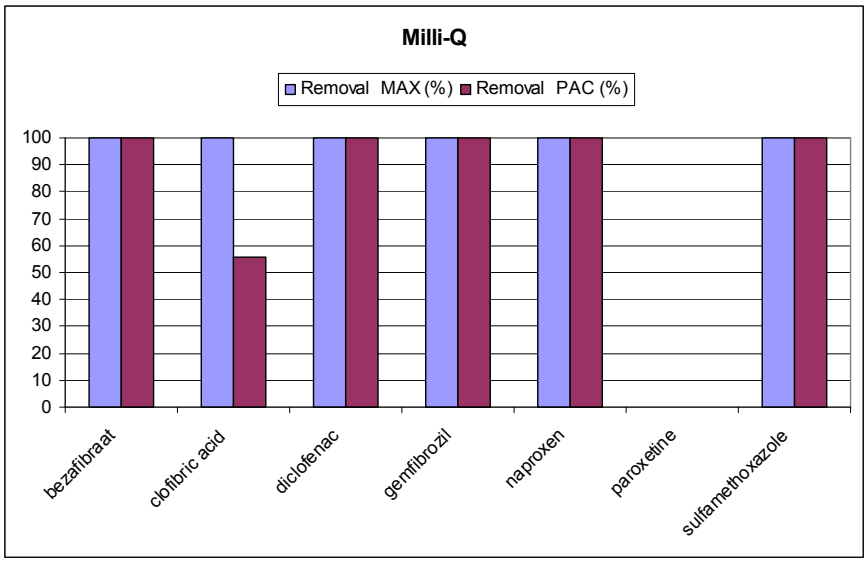


Figure VII-7: adsorption of selected pharmaceuticals in MilliQ on Oasis MAX

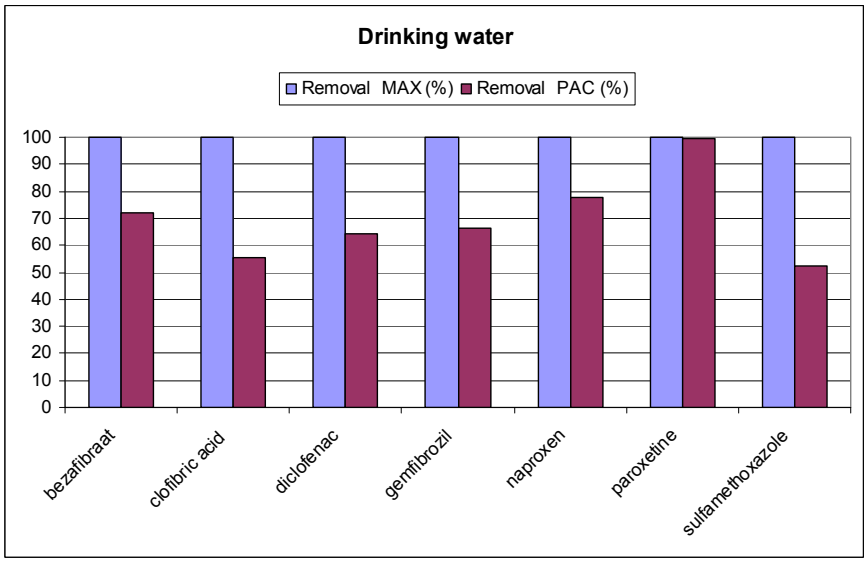


Figure VII-8: adsorption of selected pharmaceuticals in Nieuwegein drinking water on Oasis MAX

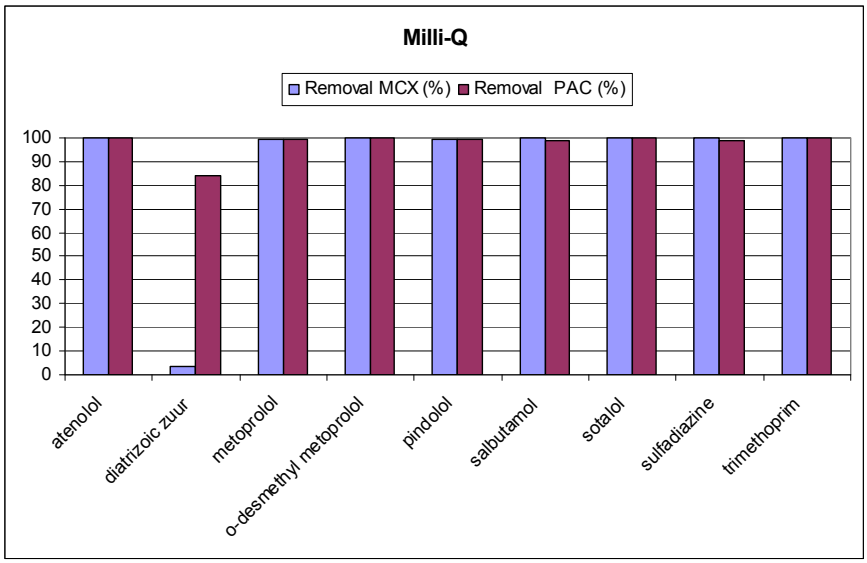


Figure VII-9: adsorption of selected pharmaceuticals in MilliQ on Oasis MCX

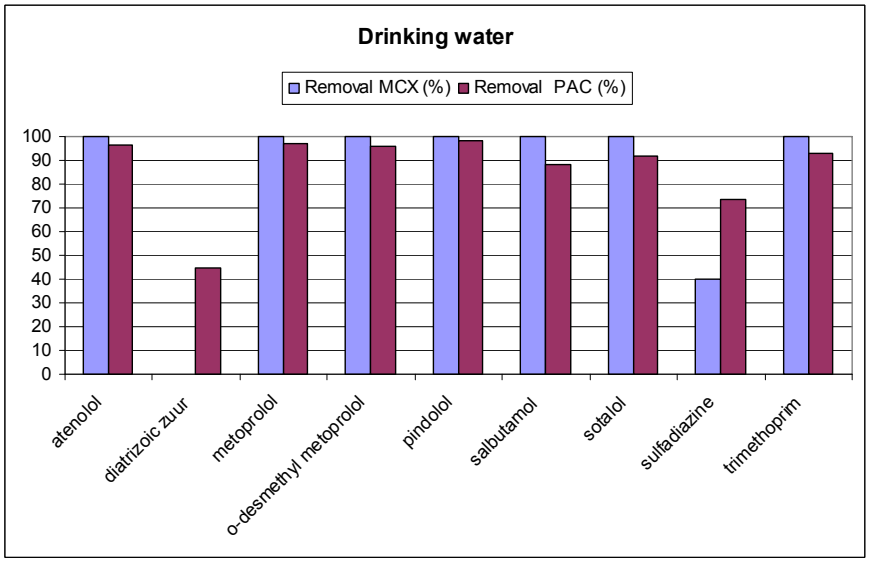


Figure VII-10: adsorption of selected pharmaceuticals in Nieuwegein drinking water on Oasis MCX

VIII Predictions based on QSAR models

For NF removal, the data-based QSAR predictions were compared with measurements in the 3 parallel 2521 membrane units (with a Desal HL 2521 TM membrane) performed at KWR at the 9th of July 2010 and 14th of June 2011. Results are shown in Figure V.1. A good agreement is found between measured and predicted data, except for trimethoprim, paracetamol and metformin.

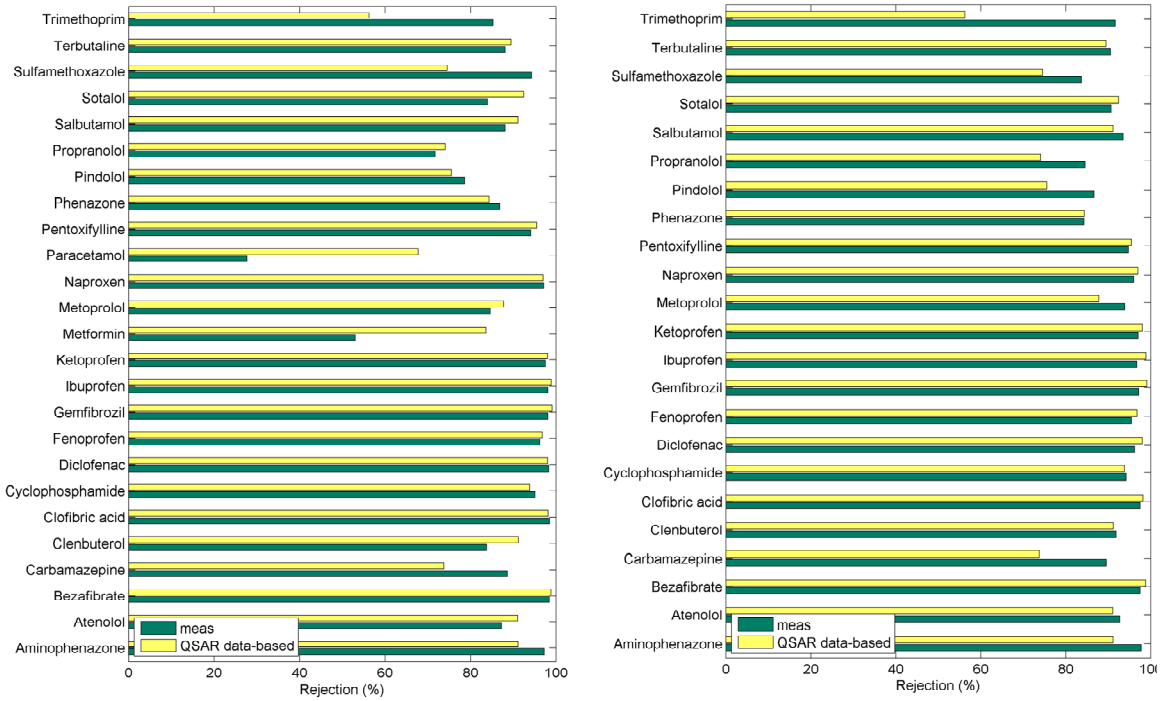


Figure VIII-1: Prediction of data-based QSAR model for Desal HL membrane compared to measured data of KWR in 2011 (left) and in 2010 (right).

For UV/ H_2O_2 systems, predicting the degradation is more difficult, because we could not find a satisfactory data-based QSAR model, whereas for the knowledge based QSAR model, only the model for the hydroxyl radical rate constant k_{OH} was accurate. Predictions obtained with this model are shown in figure VIII-2.

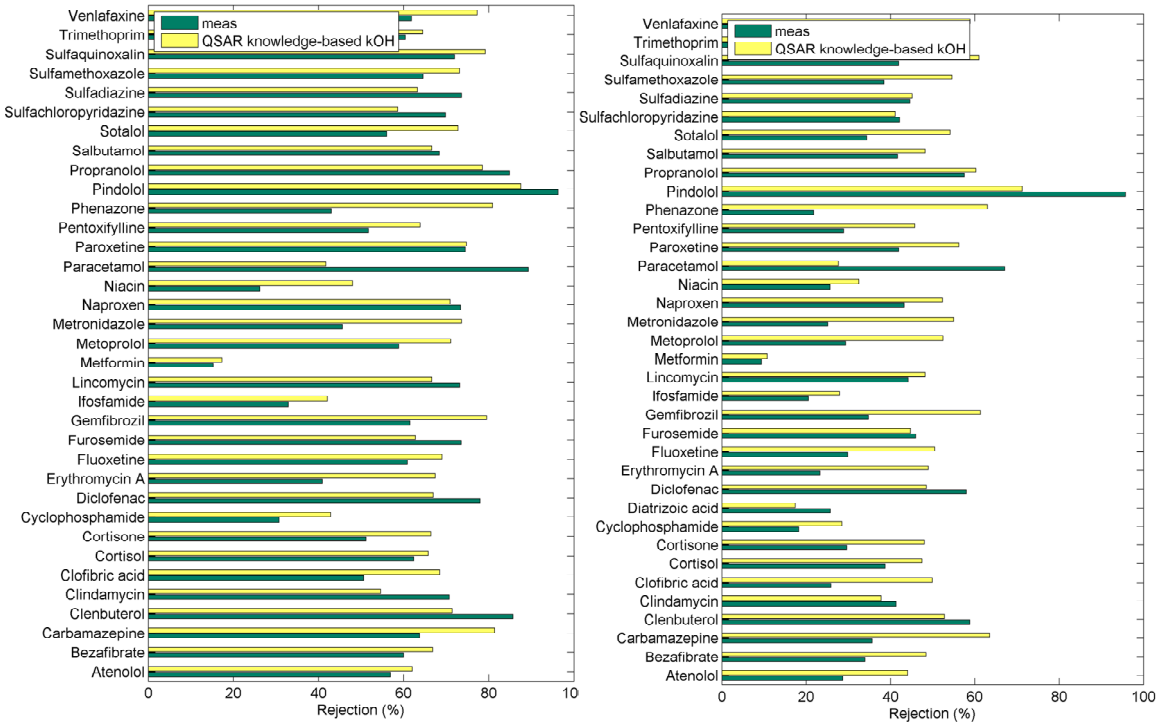


Figure VIII-2: Prediction of knowledge-based QSAR model for UV/ H_2O_2 systems compared to measured data at Dunea LP UV reactor using a ballast power of 100% (left) and 60% (right).

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