Global Water Research Coalition

Pharmaceuticals and Personal Care Products in the Water Cycle

An international review

PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN THE WATER CYCLE

AN INTERNATIONAL REVIEW

Prepared by:
Kiwa Water Research and Stowa (Netherlands)
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Global Water Research Coalition
Alliance House
12 Caxton Street
London SW1H 0QS
United Kingdom
Phone: + 44 207 654 5545
www.globalwaterresearchcoalition.net

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GLOBAL WATER RESEARCH COALITION:

GLOBAL COOPERATION FOR THE GENERATION OF WATER

Knowledge GWRC is a non-profit organization that serves as the collaborative mechanism for water research. The product the GWRC offers its members is water research information and knowledge. The Coalition will focus on water supply and wastewater issues and renewable water resources: the urban water cycle.

The founder members of the GWRC are: the Awwa Research Foundation (US), CRC Water Quality and Treatment (Australia), Kiwa (Netherlands), Sues Environment- CIRSEE (France), Stowa - Foundation for Applied Water Research (Netherlands), DVGW - TZW Water Technology Center (Germany), UK Water Industry Research (UK), Veolia- Anjou Recherché (France), Water Environment Research Foundation (US), Water Research Commission (South Africa), WaterReuse Foundation and the Water Services Association of Australia.

These organizations are all in charge of a national research program addressing the different parts of the water cycle. They have provided the impetus, credibility, and initial funding for the GWRC. Each brings a unique set of skills and knowledge to the Coalition. Through its member organisations GWRC represents the interests and needs of 500 million consumers.

The Global Water Research Coalition is affiliated with the International Water Association (IWA). The GWRC was officially formed in April 2002 with the signing of the partnership agreement at the International Water Association 3rd World Water Congress in Melbourne. With the US Environmental Protection Agency a partnership agreement was signed in July 2003.

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PREFACE

The issue of pharmaceuticals (PhAC) and personal care products (PCP) and their residues is part of the research agenda of most of the members of the Global Water Research Coalition (GWRC). It is on the priority list of GWRC.
The board of the GWRC decided in 2003 to start a project with the aim to review the occurrence and assess the risks of PhAC and PCP in the water cycle and to organise a workshop to develop a phased research strategy. This project was carried out by STOWA (project management) and Kiwa Water Research (project execution). All GWRC members contributed to the project by funding or providing expert knowledge about this issue.

This report was prepared by Leo Puijker and Margreet Mons (Kiwa). Quality assurance was conducted by the members of the GWRC Project Steering Group: Michel Gilbert, Susan Glassmeyer, Marie-Laure Janex-Habibi, Djanette Khiari, Jami Montgomery, Bert Palsma, Frank Sacher and Gordon Wheale. John Fawell has reviewed the English text.

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INTRODUCTION

1.1 BACKGROUND

Concern regarding the occurrence and effects of pharmaceuticals in the water system has been growing since the late 1990s. A number of studies have shown that pharmaceuticals (PhAC) and personal care products (PCP) are present in effluents of wastewater treatment plants and the receiving surface water. Since 1995 an increasing number of studies have been carried out in a.o. Germany, United Kingdom, the Netherlands, Denmark and the United States on the occurrence and effects of PPCPs (a.o. Stumpf *et al.,* 1996, Heberer and Stan, 1997, Ternes, 1998, Ternes *et al.*, 1998, Halling-Sørensen *et al.,* 1998, Buser and Muller, 1998, Sacher *et al.,* 2001, Ternes and Hirsch, 2000, Mons *et al.,* 2000, Ternes, 2001, Kolpin *et al.,* 2002, Mons *et al.,* 2003). A wide variety of PhAC and some PCP have been reported starting with compounds like the lipid regulating agent clofibric acid and salicylic acid and subsequently synthetic hormones, antibiotics, analgesics, anti-epileptics, β-blockers, antiseptics and X-ray contrastmedia.

Different studies and literature reviews have focussed on the use, emissions, ecotoxicity, and removal during water treatment processes and human health aspects of PhAC in drinking water (Derksen *et al.,* 2002, Derksen and Lahr, 2003, Snyder *et al.,* 2003, Versteegh *et al.*, 2003).

1.2 OBJECTIVE OF THE LITERATURE REVIEW

The objective of this literature review is to:

- summarise existing data;
- evaluate the occurrence and effects of PhAC and PCP in the water cycle;
- identify knowledge gaps; and to
- express the needs for additional research.

Although the scope of the study was originally on both groups of compounds the accent of this review is onto PhAC since only few data for are available for PCP compared to a relative large database for many PhAC.

This review will form the basis for a GWRC research strategy.

2

EMISSION OF PHAC AND PCP

There are four main sources and emission routes for PhAC and PCP to the environment (Derksen and Lahr, 2003):

1. Effluents and sludge from municipal wastewater treatment plants;
2. Disposals of unused PhAC;
3. Manure containing veterinary pharmaceuticals;
4. Industrial wastewater and solid waste from the production of PhAC and PCP.

The amount of pharmaceuticals discharged by producers is usually low (1-5% of the total production), compared to other industries. Stan *et al*. (1994) and Ternes (1998) concluded that the concentrations of pharmaceuticals and their metabolites observed in water samples originated from therapeutic use, as was indicated by their widespread distribution in municipal wastewater treatment plants.

A large variety of PhAC are used for human and animal health: for example in the Netherlands about 850 active ingredients are used in 12,000 registered products, and about 200 veterinary pharmaceuticals in 2,500 products (Derksen and Lahr, 2003). These numbers will differ between countries. Table 1 lists the main classes of PhAC and some PCP and the most typical representatives of these classes.

TABLE 1 **MAIN CLASSES OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS.**

Pharmaceuticals		
Analgesics, antipyretics, antiphlogistics, antiinflammatories, antirheumatics		
acetylsalicylic acid* diclofenac dimethylaminophenazone* fenoprofen	ibuprofen* indometacine ketoprofen* naproxen*	paracetamol phenazone propyphenazone
Antibiotics		
amoxicillin* cephalexin ciprofloxacin clarithromycin clindamycin doxycyclin erythromycin*	anhydro-erythromycin flumequin* lincomycin* mebendazole nitrofurantoin* oleandomycin oxytetracyclin	oxolinic acid* roxithromycin sulfachlorpyridazine* sulfadimethoxine* sulfamethoxazole* sulfaquinoxaline* trimethoprim
*Veterinary antibiotics**		
dimetridazole monensin narasin		
Antiepileptics		
carbamazepine primidon		

ANTINEOPLASTIC DRUGS		
CYCLOPHOSPHAMIDE IFOSFAMIDE		
BETA BLOCKERS		
ATENOLOL BISOPROLOL BETAXOLOL	METOPROLOL PINDOLOL PROPRANOLOL	SOTALOL
FIBRATES/LIPID-LOWERING AGENTS(ANTIHYPERLIPIDAEMICS)		
BEZAFIBRATE CLOFIBRIC ACID[A)] ETOFIBRATE	FENOFIBRATE FENOBRIC ACID[B)] GEMFIBROZIL	PENTOXIPHYLLINE SIMVASTATIN
X-RAY CONTRAST MEDIA		
AMIDOTRIZOIC ACID IODIPAMIDE IOHEXOL IOMEPROL	IOPAMIDOL IOPROMIDE IOPANOIC ACID IOTALAMIC ACID	IOXAGLIC ACID IOXITALAMIC ACID
TRANQUILLIZERS		
DIAZEPAM		
BRONCHOLYTICS		
SALBUTAMOL CLENBUTEROL TERBUTALINE		
COCCIDIOSTATICS*		
AMPROLIUM MONENSIN	NICARBAZINE SALUINOMYCINE	
ANTIPARASITICS*		
FLUBENDAZOL IVERMECTIN		
PERSONAL CARE PRODUCTS		
NITROMUSKS		
MUSK KETONE MUSK XYLENE		
POLYCYCLIC MUSKS		
GALAXOLIDE TONALIDE CELESTOIDE		
ANTIBACTERIAL AGENTS		
TRICLOSAN		

***) Pharmaceutical has both human and veterinary application**

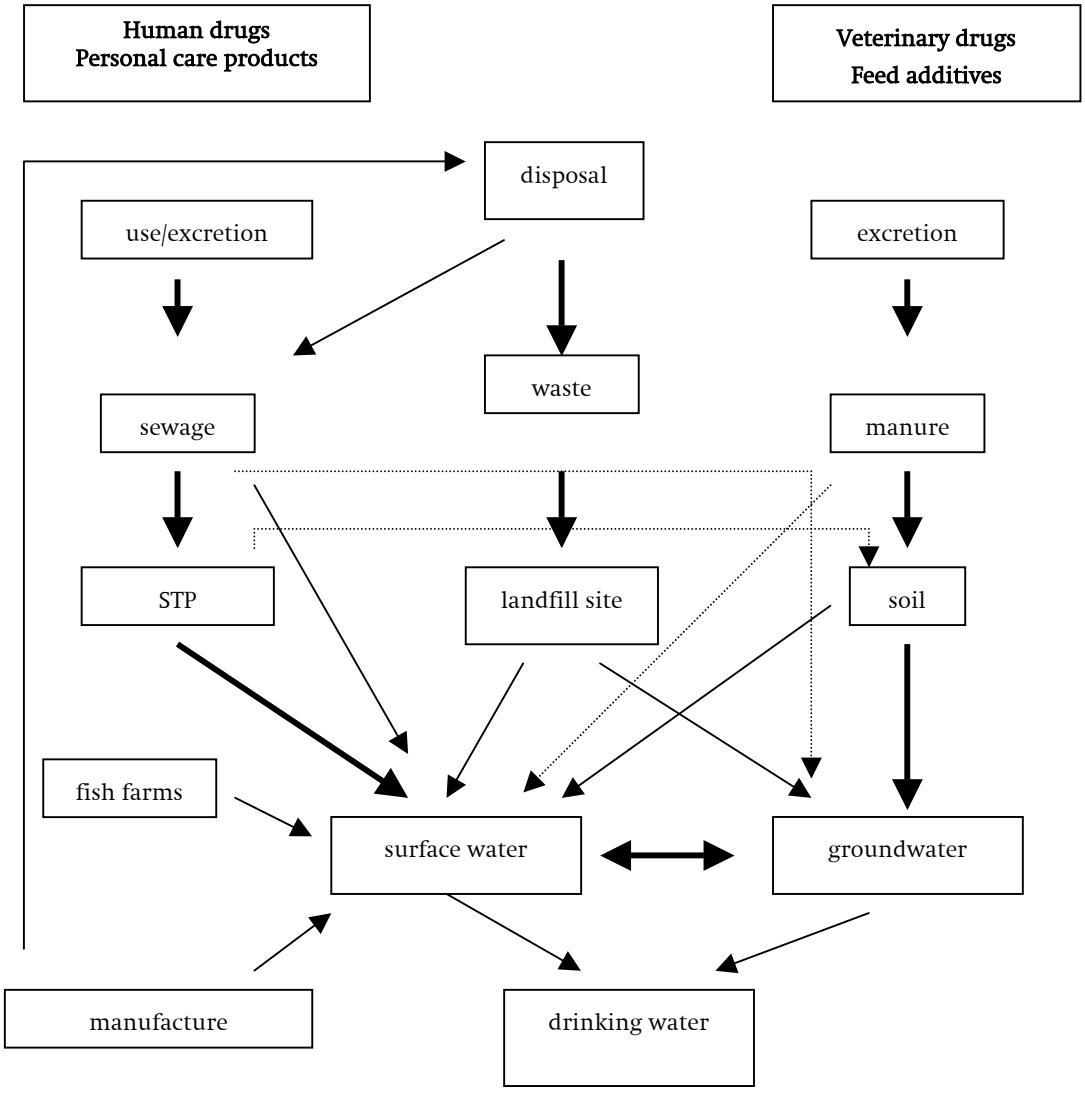
a) metabolite of clofibrate b) metabolite of fenofibrate

Information about the use or consumption is not usually publicly available. Total consumption of pharmaceuticals in human medicine has been investigated in different countries but the amounts are often expressed in monetary value or the number of prescriptions. The amounts of active ingredients are mostly unknown. For over-the-counter drugs (OTC) it is even more difficult to obtain use data or sales data. It is possible to buy some databases giving the amounts produced per year in a given country, but generally data on the most widely used pharmaceuticals are hard to obtain. However, some information is available: for example the total use of analgesics in the Netherlands amounts 200,000 kg/year (å 14 g/person/year), anti-epileptics, antibiotics and antihyperlipidaemics approximately 10,000 kg/year. There are differences between countries, which is to be expected.

For some personal care products, like synthetic musks, estimations have been made of the production and use. The daily use in Europe of musk ketone, musk xylene, AHTN (Tonalide™) and HHCB (Galaxolide™) was estimated at 0.5 – 10 mg per person (Balk, 1998). For most of the PCP data are not available.

The fate of veterinary and human pharmaceuticals following excretion differs considerably. In general municipal wastewater and, therefore, human pharmaceuticals have to pass sewers and sewage treatment prior to entering rivers of streams. Veterinary pharmaceuticals may be more likely to contaminate soil and groundwater when liquid manure is used for top soil dressing. After rainfall, surface water can be polluted with veterinary pharmaceuticals by run-off from fields or agricultural areas treated with livestock slurries.
The fate of pharmaceuticals in the environment is presented in figure 1.

FIGURE 1 **SOURCES AND FATE OF PHAC AND PCP IN THE ENVIRONMENT (TERNES, 2001).**



2.1 SELECTION OF PRIORITY SUBSTANCES

Priority substances for monitoring can be selected on the basis of total use, analytical feasibility, degradability, ecotoxicological risk, human health risks or representation of a group of pharmaceuticals.
Lists of priority substances will not necessarily be the same for different countries.

2.2 SUMMARY AND CONCLUSIONS

There are only few data readily available of the annual production or use of pharmaceuticals. If there are data, for example within the industry, these data are not made public.

The relative contributions of the various emission sources are not precisely known. Effluents from WWTPs and untreated wastewater are the most important sources for human pharmaceuticals. The quantitative contributions of veterinary pharmaceuticals, for example from fish or livestock farming, and emissions from industrial production sites are unknown.

3

OCCURRENCE OF PHAC AND PCP IN THE WATER CYCLE

Studies on the occurrence of PhAC and some PCP in the water cycle have been carried out in Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Great-Britain, Greece, Italy, the Netherlands, Sweden, Spain, Switzerland and the United States (Halling-Sørensen (1998), Daughton & Ternes (1999), Ternes *et al*., 1999, Kümmerer (2001), Daughton & Jones-Lepp (2001), Derksen *et al*. (2002), Heberer (2002) and Kolpin *et al.,* 2002)). Many data on occurrence were also presented at the POSEIDON and ENVIRPHARMA symposia in April and November 2003. This chapter will not present all of the individual research data published, but a summary of the information from these publications is presented to give an overview on the occurrence data in sewage effluent, surface water, groundwater and drinking water.
Where sources other than the above publications were used, their reference is also presented.

3.1 WASTEWATER

PhAC and PCP are invariably present in influents and effluents of wastewater treatment plants (WWTP).

ANALGESICS

The most frequently detected representatives of this class of pharmaceuticals in sewage water are acetylsalicylic acid, diclofenac, ibuprofen, naproxen, paracetamol and phenazone.
Median concentrations in WWTP effluent are in the range of 160-810 ng/l. Maximum concentrations can be as high as 600-6000 ng/l.

ANTIBIOTICS

Frequently detected antibiotics in sewage effluent are amoxicillin, ciprofloxacin, erythromycin, indometacine, oxytretracyclin, sulfamethoxazole and trimethoprim.
Median concentrations in WWTP effluent are in the range of 300-2500 ng/l, but maximum concentrations can be as high as 6000 ng/l.

ANTI-EPILEPTICS

Of all pharmaceuticals investigated, the anti-epileptic carbamazepine is one of the most frequently detected.
Median concentrations in WWTP effluent are in the range of 800-1310 ng/l, but maximum concentrations can be as high as 6300 ng/l.

ANTI-NEOPLASTIC AGENTS

Frequently investigated anti-neoplastic agents are cyclophosphamide and ifosfamide. Maximum concentration detected in domestic wastewater is 20 ng/l. Concentrations in hospital wastewater are usually many times higher than in domestic wastewater.
Concentrations of 20-4500 ng/l have been detected in hospital wastewater. Aherne *et al* (1990) detected concentrations of the anti-neoplastic agent bleomycin of 11-19 ng/l in WWTP effluent.

BETA-BLOCKERS

Frequently detected beta-blockers in WWTP effluent are metoprolol, propanolol, betaxolol, bisoprolol, nadolol and sotalol. In WWTP effluent concentrations of 700 ng/l (median) up to 2200 ng/l (maximum) have been detected.

FIBRATES/LLIPID REGULATORS (ANTIHYPERLIPIDAEMICS)

Bezafibrate, clofibric acid, fenofibric acid and gemfibrozil are frequently detected. In WWTP effluent median concentrations are between 400-2200 ng/l. Maximum concentrations are in the range of 1000-7000 ng/l (presentation Alder at POSEIDON symposium).

TRANQUILLISERS

Diazepam is a tranquilliser that has frequently been included in studies. Maximum concentration detected in WWTP effluent is 40 ng/l.

X-RAY CONTRAST MEDIA

X-ray contrast media are very persistent and therefore frequently detected in high concentrations in WWTP effluent and hospital wastewater. Major representatives of this class of pharmaceuticals frequently detected are amidotrizoic acid, iopamidol, iopromide and iomeprol. In WWTP effluent and hospital wastewater concentrations of up to 11,000 ng/l have been detected.

ESTROGENS

The most intensively studied endocrine disrupting pharmaceutical is 17-α-ethinylestradiol (EE2), major component of the contraceptive pill. Concentrations detected in WWTP effluent are usually in the range of 2-20 ng/l. The maximum concentration reported was 62 ng/l (Stumpf *et al.,* 1996).

PERSONAL CARE PRODUCTS

The definition of personal care products is very wide. Two groups of synthetic musks, the 'nitromusks' and the 'polycyclic' musks are the most extensively studied. The nitromusks musk ketone and musk xylene have been detected in WWTP effluent in concentrations of 25-410 ng/l.
Galaxolide, Tonalide and Celestoide are the most frequently detected polycyclic musks in water. Median concentrations in WWTP effluent are about 6600 ng/l, 2100 ng/l and 120 ng/l for Galaxolide, Tonalide and Celestoide respectively, but maximum concentrations reported were up to 13,300 ng/l, 4360 ng/l and 210 ng/l respectively (Fromme, 2001).
The anti-bacterial agent Triclosan has been detected in WWTP effluents in the United Kingdom and The Netherlands (Kanda *et al.,* 2003, pers. comm. RIVM, 2003).

3.2 SURFACE WATER

Contamination of surface water with human pharmaceuticals and personal care products can occur via emissions from industry and from the effluent from WWTPs. Emissions with veterinary pharmaceuticals to surface water mainly occur as a consequence of run-off from farmland (see chapter 2). There are only few pharmaceuticals that are only applied in veterinary medicine and many have an application in both human and veterinary medicine. When a pharmaceutical is detected in surface water it may, therefore, be difficult to determine whether its presence is from human use or use in cattle livestock. In this report Therefore no distinction has been made between the occurrence of human and veterinary pharmaceuticals.

ANALGESICS AND ANTIHYPERTENSIVES

The most frequently detected analgesics and antihypertensives in surface water are diclofenac, ibuprofen, codeine, cimetidine and phenazone. Median concentrations in surface water are usually in the range of 50-1000 ng/l for diclofenac, ibuprofen and codeine, and 20-100 ng/l for other analgesics.

ANTIBIOTICS AND ANTIBACTERIALS

Antibiotics frequently detected in surface water are erythromycin-H_2O (metabolite of erythromycin), lincomycin, roxithromycin, sulfamethazine, sulfamethoxazole and trimethoprim. Median concentrations in surface water are usually in the range of 20-100 ng/l. Maximum concentrations can be as high as 1700 ng/l.

ANTI-EPILEPTICS

Carbamazepine is not removed during sewage treatment to any great extent so it is frequently found in surface water. Median concentrations in surface water are usually between 20-300 ng/l, but maximum concentrations can be as high as 1000-2000 ng/l.

ANTI-NEOPLASTIC AGENTS

Ifosfamide and cyclophosphamide have not been detected in surface water. However, Aherne et al. (1990) detected concentrations of 5-17 ng/l of the anti-neoplastic agent bleomycine in surface water.

BETA-BLOCKERS

In surface water the main beta-blockers detected were metoprolol, propanolol, bisoprolol and sotalol. Median concentrations in surface water are usually between 20-20 ng/l, but maximum concentrations can be as high as 1000-2000 ng/l.

ANTIDIABETICS

Metformin was found in the U.S. at an estimated maximum concentration of 150 ng/l (average recovery < 60%).

FIBRATES/LLIPID REGULATORS/ANTIHYPERLIPIDAEMICS

The lipid regulators most frequently detected in surface water are bezafibrate, clofibric acid (metabolite of clofibrate), fenofibric acid and gemfibrozil. Median concentrations are between 20-200 ng/l, but maximum concentrations can be as high as 2000-3000 ng/l for gemfibrozil and bezafibrate, and 300 ng/l for fenofibric acid.

TRANQUILIZERS AND ANTIDEPRESSANTS

Diazepam has not been detected in surface water but. Ffluoxetine (antidepressant, Prozac) was found in one surface water sample in the U.S. Geological Survey at an estimated concentration of 12 ng/l (average recovery < 60%).

X-RAY CONTRAST MEDIA

The most frequently detected X-ray contrast media in surface water are amidotrizoic acid, iopamidol, iomeprol and iopromide. In surface water median concentrations are usually between 50-300 ng/l. Iohexol and ioxitalamic acid are also quite frequently detected, but usually in lower concentrations than the other X-ray contrast media, 10-100 ng/l.

ESTROGENS

17-α-Ethinylestradiol (EE2) has been detected incidentally at concentrations to 5 ng/l in German surface water or in surface water in the Netherlands (Wenzel *et al.,* 2003). In the United States Geological Survey it was found in 15,7 % of the samples with a median concentration of 73 ng/l.

PERSONAL CARE PRODUCTS

The nitro musks musk ketone and musk xylene have been detected in surface water in concentrations of 1-23 ng/l.Galaxolide, Tonalide and Celestoide are the most frequently detected polycyclic musks in water. In surface water in Western Europe the median concentration of both Galaxolide and Tonalide is 70 ng/l (Balk *et al*., 2001). Concentrations of Celestoide are usually lower, 2-8 ng/l. Maximum concentrations can be above 10,000 ng/l in surface water receiving high percentages of treated wastewater (Heberer *et al*., 1999, as cited by Daughton and Ternes, 1999). Triclosan has been detected in surface water at concentrations of 50-150 ng/l (Daughton & Ternes, 1999). In the United States concentrations triclosan detected ranged from 0.14 μg/l (average) up to 2 μg/l (maximum) (Kolpin *et al*., 2002).

3.3 GROUNDWATER

Compared to WWTP effluent and surface water, groundwater is relatively unaffected by PhAC. The number of compounds detected and their concentrations are much lower than in sewage effluent and surface water. However, leakage of wastewater from sewers can influence groundwater quality considerably (Sacher pers. comm. 2003).
Maximum concentrations of PhAC detected in groundwater are presented in Table 2.

TABLE 2 **MAXIMUM CONCENTRATIONS OF PHARMACEUTICALS DETECTED IN GROUNDWATER.**

PPCP	Max conc. detected (ng/l)	Reference
Analgesics		
Phenazone	25	Sacher *et al.* (2001)
Ibuprofen	43	Mons *et al.* (2003)
Propyphenazone	1465	Heberer *et al.* (1997)
Antibiotics		
Erythromycin	49	Sacher *et al.* (2001)
Erythromycin	20	Versteegh *et al.* (2003)
Sulfamethoxazole	410	Sacher *et al.* (2001)
Fibrates/lipid regulators		
Bezafibrate	190	Ternes, (2001)
Clofibric acid	7300	Heberer *et al.* (1998)
Diclofenac	590	Sacher *et al.* (2001)
Fenofibrate	45	Heberer *et al.* (1997)
Gemfibrozil	340	Heberer (2002)
Anti-epileptics		
Carbamazepine	900	Sacher *et al.* (2001)
Beta blockers		
Sotalol	560	Sacher *et al.* (2001)
X-ray contrast media		
Amidotrizoic acid	1100	Sacher *et al.* (2001)
Iopamidol	2400	Ternes & Hirsch 2000
Iopromide	210	Ternes & Hirsch 2000
Iothalamic acid	49	Ternes & Hirsch 2000
Ioxithalamic acid	10	Ternes & Hirsch 2000

3.4 DRINKING WATER

Data on the occurrence of pharmaceuticals in drinking water have only been published for Germany, Italy and The Netherlands. Qualitative data for clofibric acid have been published for the UK (Fielding *et al*., 1981 as cited by Environment Agency, 2000).

Few pharmaceuticals have been identified in domestic drinking water. Stan *et al.* (1994), Stumpf *et al.* (1996), Heberer *et al.* (1998) and Ternes *et al.* (1999) found several pharmaceuticals in German drinking water in the lower ng/l-range. Recently more data on the Dutch situation have been published, including data on occurrence in drinking water (Mons *et al.*, 2003, Versteegh *et al.*, 2003).

Although there are some exceptions, the majority of the samples analysed in the different investigations found no pharmaceuticals. Where they were found, concentrations detected in drinking water were usually below 10-50 ng/l. Table 3 presents the pharmaceuticals detected in drinking water and the maximum concentration reported.

TABLE 3 **MAXIMUM CONCENTRATIONS OF PHARMACEUTICALS DETECTED IN DRINKING WATER.**

PhAC	Max. conc. detected (ng/l)	Reference
Analgesics		
acetylsalicylic acid	13	Mons *et al.*(2003) Versteegh *et al.* (2003)
Diclofenac	6	Stumpf *et al.*, (1996)
Ibuprofen	23	Stumpf *et al.* (1996) Ternes *et al.* (2001b) Mons *et al.* (2003)
Phenazone	50	Ternes (2001b) Mons *et al.* (2003)
Antibiotics		
Lincomycine	21	Mons *et al.* (2003)
Sulfamethoxazole	40	Mons *et al.* (2003) Versteegh *et al.* (2003)
Anti-epileptics		
Carbamazepine	90	Ternes (2001b) Mons *et al.* (2003) Versteegh *et al.* (2003)
Fibrates/lipid regulators		
Bezafibrate	27	Stumpf *et al.* (1996)
clofibric acid	170	Stan *et al.* (1994) Stumpf *et al.* (1996) Heberer & Stan (1997) Zuccato (2000) Versteegh *et al.* (2003)
fenofibric acid	42	Ternes (2001b)
X-ray contrast media		
amidotrizoic acid	85	Ternes (2001b) Mons *et al.* (2003)
Iopamidol	79	Ternes (2001b) Mons *et al.* (2003)
Iopromide	86	Ternes (2001b)
Tranquilizers		
Diazepam	23.5	Zuccato (2000)
Veterinary pharmaceuticals		
Tylosin	1.7	Zuccato (2000)

3.5 ANALYTICAL METHODS

More than 100 different PhAC have been measured in the various monitoring programs. Analyses have usually been carried out using reversed phase HPLC-MS-MS or with GC-MS after chemical derivatisation. In order to achieve sufficiently low detection limits, pre-concentration techniques have been used, mostly based on off-line solid phase extraction or in line on-column adsorption. The detection limits vary from 1 to 50 ng/l. Recoveries vary between 50 and 100 %, with an exception of the polar X-ray contrast media with a recover of less than 10 % for diatrizoate. The standard deviation (reproducibility) is generally better than 20 %. Since accurate analytical techniques have not been available for a long time, data, particularly from early work and results for wastewater and sludge, can be less accurate. The literature on analytical methods for PhAC in soils, sediments and sludge was reviewed by Díaz-Cruz *et al.* (2003). Detailed descriptions of the analytical methods for water samples are given in Ternes *et al.* (1998), Sacher *et al.* (2001), Schrap *et al.* (2003) and Van Leerdam *et al.*, (2004).

3.6 SUMMARY AND CONCLUSIONS

Many data are available on the occurrence of PhAc and some PCP in sewage effluent, surface water, and to a lesser extent in groundwater and drinking water. Occurrence data from European countries and the United States are mostly in line with each other. Few or no data are availablefrom other parts of the world.
Pharmaceuticals and personal care products are frequently detected in high concentrations in WWTP effluent and surface waters. Concentrations are in the range of 1000-10,000 ng/l for WWTP effluent and 100-1000 ng/l for surface water. In hospital wastewater concentrations of especially X-ray contrast media, antibiotics and anti-neoplastic agents can be much higher than in regular domestic wastewater. Groundwater is less affected; concentrations are usually varying from 10-100 ng/l. There are some exceptions where higher concentrations have been detected, possible as a result of leakage from sewers.
Very low levels (1-100 ng/l) of different PhAC have been found in drinking water.
There are very few data available on the occurrence of personal care products in groundwater and drinking water.

The most predominant pharmaceuticals in water are diclofenac, ibuprofen, naproxen, bezafibrate, clofibric acid, carbamazepine, erythromycin, sulfamethoxazole and some X-ray contrast media, such as iopamidol, iopromide and amidotrizoic acid (diatrizoate).

Most data have resulted from individual research projects that have been conducted as one-off samples. A Europe -wide integrated monitoring program on PhAC and PCP, with frequent monitoring in different types of water, has not been conducted until now. Results from EU-research projects like ENVIRPHARMA, ERAVMIS and POSEIDON are the basis for monitoring programs in the future.

Further development of analytical techniques for PhAC and PCP is required to improve the performance characteristics for a number of selected compounds, e.g. the recovery for some polar compounds and the analysis of wastewater and sludge. It is important that properly validated analytical methods are implemented in monitoring programs, along with frequent monitoring.

4

RISKS FOR ECOSYSTEMS

4.1 AVAILABLE ECOTOXICITY DATA FOR PHARMACEUTICALS

Ecotoxicity data have been evaluated by Halling-Sørensen *et al*. (1998), Daughton & Ternes (1999), Webb (2001), Derksen *et al.* (2002), Brooks *et al.* (2003) and Schrap *et al*. (2003) among others. A summary of their findings is presented below.

ACUTE TOXICITY

Most information on ecotoxicological effects of PhAC is available from acute toxicity data. Over 90% of the acute toxicity studies have an effect concentration > 1 mg/l. This shows that most PhAC have a low acute toxicity for aquatic organisms. PhAC with acute ecotoxicological effects at concentrations < 1 mg/l are nitro musks, amino nitro musks and substances that are used for treating the human nervous system, such as anti-depressants, antipsychotics and anaesthetics. Bacteria, cyanobacteria and algae can be relatively sensitive to antibiotics.

CHRONIC TOXICITY

Data on chronic ecotoxicity are limited. If data are available they are mainly from reproduction tests with Daphnids, or growth inhibition tests with algae or cyanobacteria. Derksen and Lahr (2003) found data for 25 pharmaceuticals. Chronic effect concentrations are at the level of a few to a few tens of µg/l. The values are at the upper limit of the concentration ranges for the occurrence in surface water. Chronic effects therefore cannot be excluded for some aquatic life. These effects will depend on a range of factors, including the level of organic matter, which can also reduce the toxicity and availability of substances to aquatic organisms.

SPECIFIC TOXICITY

Most pharmaceuticals are designed to target specific metabolic pathways in humans and animals, but they can have unknown effects on metabolic systems of nontarget organisms, especially invertebrates.

Recent evidence shows that pharmaceuticals with highly specific mechanisms, like selective serotonin reuptake inhibitors (SSRIs, in antidepressants) can elicit profound effects at extremely low concentrations. These effects are not necessarily readily detectable but have the potential to lead to ecologic change that could be erroneously attributed to natural changes.

Daughton & Ternes (1999) give an example of the complex potential for adverse drug interactions in nontarget species. One of the mechanisms in organisms for elimination of xenobiotics is the multidrug transport system. This excretory system, also called the multixenobiotic transporter, comprises proteins that facilitate active transport of potentially toxic substances from inside cells. The toxicological significance of these non-specific transporters is in maintaining a first line defence against exposure to multiple xenobiotics. They seem to have non-specific recognition, working for many pesticides, drugs and other xenobiotics. The action of this transporter system can be inhibited by

certain PhAC such as verapamil, a cardiac pharmaceutical, and the antibiotic cyclosporine A, thereby increasing the vulnerability of the species to other xenobiotics.

DEVELOPMENT OF RESISTANCE

See chapter 5.

AVAILABLE ECOTOXICITY DATA FOR PERSONAL CARE PRODUCTS

Personal care products differ from pharmaceuticals in that large amounts can be directly introduced to the environment. Less is known about the effects of this broad class of chemicals on non-target organisms, especially aquatic organisms. Information available is mainly on musk fragrance ingredients.

Musks are very lipophilic and can therefore bioconcentrate/bioaccumulate in the environment. Concern has been raised considering developmental toxicity in aquatic organisms. Musk ambrette may play a role in damaging the nervous system (Kirschner 1997, as cited by Daughton and Ternes, 1999).

Under anaerobic conditions nitromusks can be transformed into the nitrobenzene, which can be far more toxic to aquatic organisms than the parent compound. EC_{50} values of 250 ng/l have been reported (Behecti *et al*., as cited in Daughton & Ternes, 1999).

Daughton & Ternes (1999) therefore state that more attention should be focussed on the amino nitro musks transformation products as they are more water soluble than the parent musks, still have a high bioaccumulation potential and are more toxic than the parent compounds.

4.2 ENVIRONMENTAL RISK ASSESSMENT

The EU Directives 2001/83/EC on human pharmaceuticals and 2001/82/EC on veterinary pharmaceuticals set out an environmental risk assessment in the frame of the authorisation of new medicinal products.

Directive 2001/83/EC requires an ecotoxicity assessment of the environmental risk arising from the use, the storage and the disposal before a *human pharmaceutical* is placed on the market. A draft Note for Guidance document on the environmental risk assessment has been released in 2001 by EMEA (European Medicinal Evaluation Agency). It is stated that for the environmental exposure assessment the PEC (predicted environmental concentration) has to be calculated, based on the percentage of market penetration, maximum daily dose, amount of wastewater per inhabitant and a dilution factor. If this PEC is below 0.01 µg/l (10 ng/l), and no other environmental concerns are apparent, it may be assumed that the medicinal product is unlikely to represent a risk for the environment.

Recently, a new draft Note for Guidance has been published. A new feature in this draft is that deviance from this action limit now is possible. An expert evaluation can now be conducted for other unusual ecotoxicological effects, such as endocrine disruption. However, it remains very difficult to include such effects in an environmental risk assessment.

If the PEC is > 0.01 µg/l, which will be the case for many PhAC, a Phase II environmental effect analysis should be performed, including tests for biodegradability, aquatic toxicity studies and environmental microbial toxicity studies.

The existing European Guidance document for the environmental risk assessment of *veterinary pharmaceuticals* is currently being revised in the frame of the multilateral VICH process (International Cooperation on the Harmonisation of Technical Requirements for

Registration of Veterinary Products). The first section of the two-phased VICH guidance concept was implemented in 2001. The draft VICH Phase II paper was published in mid October 2003. In Phase I, there is a decision tree with action limits to determine whether an environmental impact assessment according to phase II is required. The action level for water is 1 μg/l (1000 ng/l). If the PEC is > 1 μg/l a Phase II environmental effect analysis should be performed, including tests for biodegradability, aquatic toxicity studies and environmental microbial toxicity studies.

4.3 SUMMARY AND CONCLUSIONS

With the current knowledge for most pharmaceuticals it is not possible to make a proper estimate of the ecotoxicological risk of human pharmaceuticals to the environment. However, risks for aquatic organisms cannot be ruled out. Better data are needed on a wider range of species in studies that are relevant to the various types of water.

5

HUMAN HEALTH RISK

5.1 IN GENERAL

The presence of PhAC and PCP in the environment cannot be ignored. The risk for humans is a function of the extent of exposure. The risk at low concentrations is not well known. In particular, very little knowledge and few data on of the long-term effects of these compounds are available in the public domain, largely because of commercial confidentiality.

Different studies show that PhAC are sometimes present in drinking water at very low concentrations (concentration range from 1 – 100 ng/l). Exposure to PhAC and PCP can also take place during recreation in surface water. However the low frequency of this exposure in combination with the low amount of water ingested (<100 ml) makes this route of exposure of negligible importance.

5.2 HEALTH RISK EVALUATION & REGULATION

At this moment there is no regulatory guidance on how to assess the risks for human exposure to low concentrations of pharmaceuticals in drinking water.

Evaluations of the human risk have been made before by Richardson and Bowron (1985), Christensen (1998), Mons *et al.,* (2000), Webb (2001) and Schulman *et al.* (2002). They all concluded that no appreciable risk for humans exists at the low levels measured in drinking water.

Webb (2001), Webb *et al.* (2003) and Mons *et al*., (2003) estimated the lifetime intake (70 years) of pharmaceuticals via drinking water (2 litres daily), represented as I_{70} values. They conclude that these I_{70} values, representing lifetime consumption, are far below the daily therapeutic dose. Mons *et al*. (2003) calculated that lifetime consumption of drinking water with these concentrations of pharmaceuticals would result in a maximum consumption of 5% of one (1) daily therapeutic dose.

Recently Versteegh *et al.* (2003) calculated provisional 'no effect levels' for a number of pharmaceuticals detected in Dutch drinking water, based on acceptable daily intake (ADI) or maximum residue levels (MRL) for veterinary pharmaceuticals in milk (see Table 4). The measured concentrations in drinking water are a factor 500 to 10^6 lower than the calculated (provisional) no effect levels.

TABLE 4 PROVISIONAL NO EFFECT LEVELS FOR DRINKING WATER FOR SOME PHARMACEUTICALS (VERSTEEGH ET AL., 2003).

PHARMACEUTICAL	PROVISIONAL 'NO EFFECT LEVEL' DRINKING WATER (NG/L)
ACETYLSALICYLIC ACID	25,000
BEZAFIBRATE	35,000 [A)]
BISOPROLOL	1,000 [A)]
CARBAMAZEPINE	50,000 [A)]
ERYTHROMYCIN	15,000
DICLOFENAC	7500 [A)]
CLOFIBRIC ACID	30,000 [A)]
METOPROLOL	50,000 [A)]
SULPHAMETHOXAZOLE	75,000
PARACETAMOL	150,000
FENOFIBRATE	50,000 [A)]
IBUPROFEN	150,000 [A)]
CHLOROAMPHENICOL	LOQ
LINCOMYCIN	30,000
PHENAZONE	125,000 [A)]
IOPAMIDOL	415×10^9 [A)]
AMIDOTRIZOIC ACID	250×10^9

a): provisional drinking water limit: If no ADI or MRL was available a provisional ADI was determined from the lowest pharmacological effective dose and a safety factor of 100.

Although the concentrations in drinking water are very low and effects will be unlikely, some consideration will be required regarding the long-term low-level exposure.

5.3 LONG-TERM EXPOSURE TO PHAC

Possible effects of long-term exposure to pharmaceuticals have been discussed by Van Gool, (1993), Ayscough (1999), Daughton and Ternes (1999), Gezondheidsraad (2001) and Derksen *et al.* (2002). Possible effects are endocrine disrupting activity, induction of antibiotic resistance, genotoxicity, carcinogenicity and allergic reactions.
Based on the available information, Ayscought *et al. (*1999) concluded that the only pharmaceutical for which subtle *endocrine disrupting* effects have been currently demonstrated in laboratory studies at environmental relevant concentrations is 17α-ethinylestradiol.

The induction of microbial *resistance to antibiotics* by exposure to environmental concentrations is a subject that remains controversial. Microbial resistance to antibiotics has been noted in surface water and sewage effluent, but Ayscough *et al* (1999) concluded that the most likely cause is not the induction of resistance caused by exposure to low levels of antibiotics, but the excretion of resistant organisms by humans and animals receiving antibiotics. A recent study of the German Umweltbundesambt performed at the University of Würzburg (Ohlsen, 2001) confirmed that low concentrations of antibiotics in the environment did not exert any effect on the transfer of 'resistance' plasmids between bacterial populations.

Genotoxic activity has been demonstrated in untreated wastewater from hospitals in a few studies (Giuliani, 1996, Steger-Hartmann *et al*., 1997, Hartmann, 1998). Ayscough (1999) and Derksen *et al*. (2001) list some studies on pharmaceuticals that have demonstrated a genotoxic and/or carcinogenic potential. However, Ayscough (1999) concluded that the

hospital wastewater is likely to undergo significant dilution on passage to the sewage treatment plant, thereby reducing the genotoxic potential to negligible levels.

Antibiotics are one class of pharmaceuticals, some of which are known to cause *allergic reactions* in humans. Although it is often a characteristic of allergic reactions that a response is elicited at very low doses, it will be very difficult to demonstrate a causal relationship between allergic reaction in humans and the presence of antibiotics in water. In particular the antibiotics that are of particular concern for allergic reactions have been looked for but not found. In addition the oral route of exposure is less likely to result in a response to very low concentrations of these compounds.

5.4 POLICY & PRECAUTIONARY PRINCIPLE

Although the concentrations in drinking water are very low, and effects in humans will be unlikely, some consideration will always be required regarding long-term low level human exposure to pharmaceuticals based on precautionary principles. The EU Drinking Water Directive (98/83/EC) states that drinking water should not contain unwanted substances and that chemical risks should be avoided.

Drinking water organisations strive towards a source water quality that permits relatively simple, natural treatment processes to assure safe and healthy drinking water. Anthropogenic substances, and certainly such substances that cannot be removed readily by simple treatment, do not belong in surface water. Lifetime exposure to low doses of chemicals might results in unwanted effects, therefore the exposure to these substances should be as low as possible. This precautionary principle is not applied on a scientific basis, but is a policy principle within the EU.

5.5 SUMMARY AND CONCLUSIONS

PhAC have been detected in drinking water. The general population can, therefore be exposed to these substances via drinking water. However, concentrations ingested are far below the daily therapeutic doses and safe levels that have been derived.

The exact human and environmental significance of PhAC with regard to subtle long-term effects are less clear as the necessary toxicity data are lacking. Based on precautionary principles exposure to these substances via drinking water should therefore be minimised.

6

RISK & RISK PERCEPTION

6.1 WHAT IS RISK?

Many definitions of the term 'risk' have been provided. All of them incorporate the words 'likelihood' or 'chance' combined with 'severeness' or 'magnitude' of the effect.
However, there are many more aspects that play a role in risk assessment, for example: the degree to which the activity is voluntary, how fairly are the benefits and burdens distributed and to what extent is the situation manageable? The risk concept therefore does not consist exclusively of objectively measurable characteristics of systems but is also a social contract, in which qualitative, social-psychological characteristics can play an important role.
The choice of admissible risk and the extent of differentiation are subject for the political domain. But when regarding risks it is of importance to keep in mind that there can be a large gap between the actual risk and the perceived risk.

6.2 WHICH FACTORS DETERMINE RISK PERCEPTION

Human beings are not particularly rational, and one way in which that is apparent is how members of the public perceive issues of risk and safety. Risk perception is influenced by complicated social, cultural and psychological factors as well as by objective information.
Individuals judge risks on the basis of how familiar they are with the risk, how likely it is that an effect will occur, how widespread the effects are and who is affected, among others.
Issues of choice and control strongly influence risk perceptions. People perceive involuntary risks whose sources they do not control as being more dangerous. Risk perception is also strongly influenced by perceptions of the relationship between those who incur the risk and those who receive the benefit.

Water has a unique role in people's emotional associations. Notions of water contamination convey threats of sickness; notions of water purity convey suggestions of health and safety.
How well a water utility was doing its job was once perceived on the basis of whether water came out of the tap-an objective, readily identifiable measure. Now, however, their view of the utility's performance is influenced more by their perceptions regarding the water quality. Because those perceptions are subjective, utilities face an increasingly difficult task in convincing the public that the water provided to them is safe.
Rising public awareness about environmental problems has magnified people's concern about the quality of water and drinking water in particular, even in the absence of any degradation of that quality.
Risk concerns are often a surrogate for many other social or ideological concerns. They may provide a rationale for actions taken as a result of other beliefs not related to risk. Pollution is often perceived as morally wrong, regardless of the level of risk or the practicality of reducing the risk.

Contributing to the complicated issue of risk perception is the difficulty that the public have in dealing with probability and uncertainty, both of which underlie determinations of risk. Presenting the same risk information in different ways influences how people perceive a situation and what actions they take. Potential losses seem larger than potential gains. Low probabilities seem greater than they are, and high probabilities seem less than they are. That may partly explain why a person buys a lottery ticket and cigarettes at the same time.

6.3 CONSEQUENCES FOR THE SUBJECT OF PHAC AND PCP

The public can be concerned about PhAC and PCP in their drinking water and the media play an important role in their beliefs. Although the media may not determine a person's belief or position on an issue, media attention determines whether a person notices or is concerned about an issue. Therefore it is important to avoid negative media attention on the topic.

In the United States and in the Netherlands lists of FAQs (Frequently Asked Questions) or Q&A (Questions & Answers) have been developed to inform the public about the topic of PhAC and PCP. Although comparison of the levels of PhAC detected in drinking water with derived safe limits shows that human effects are unlikely to occur, this information still might be not sufficient to take away the feeling of it being unsafe in the general public. After all, pharmaceuticals have been designed to have a biological effect and information on the effects of long-term exposure to low levels of PhAC is not widely available.

6.4 SUMMARY AND CONCLUSIONS

Considering the public perception of water quality the question is whether regulation of PhAC in surface water and drinking water could decrease the public concern with respect to this subject.

Experience from other counties regarding this issue should be exchanged to set up guidelines and/or a general approach for communication.

In addition the government could also play an important role in the communication strategy.

7

REMOVAL OF PHAC AND PCP IN WATER TREATMENT

During wastewater treatment there is a significant removal of PhAC and PCP. However, they are not completely removed in municipal wastewater treatment plants and treated wastewater is still a source of PhAC. In the receiving environment they can be removed from surface water by biodegradation and adsorption onto particles and sedimentation. There is a significant removal during artificial infiltration or riverbank filtration. Finally PhAC and PCP are removed by various drinking water treatment steps.

7.1 WASTEWATER TREATMENT

A literature review to the removal of PhAC and PCP in wastewater treatment plants was carried out by Derksen and Lahr (2003). They concluded that in wastewater treatment plants and sewage treatment plants a significant reduction is achieved for most of the pharmaceuticals by degradation or adsorption onto the sludge. However, since there is often no direct relation between sampling of influents and effluents of WWTPs the data for removal are not very accurate. Antibiotics do not seem to reduce the level of biodegradation. A shorter retention time caused by rainfall can cause a large reduction of the removal capacity. Since contaminated sludge is one of the outputs of the WWTP attention must be paid to sludge as a possible source of contamination.

The fate of 17α-ethinylestradiol and other natural hormones (estrone, estradiol) was investigated in mechanical and biological sewage treatment as well as in sewage sludge treatment at a municipal German sewage treatment plant (Andersen *et al.*, 2003). They found high elimination efficiencies for natural hormones in denitrifying and aerated nitrifying tanks (> 98 %). More than 90% of 17α-Eethinylestradiol was removed under nitrifying conditions.

Membrane-bio-reactors, in which biodegradation and removal of particles by filtration are combined, are also effective in removing PhAC.

Additional recent information has been presented during “ENVIRPHARMA”: the European conference on human and veterinary pharmaceuticals in the environment, held in Lyon, April, 2003. The removal in sewage treatment plants differs considerably for the individual pharmaceutical and by differing process conditions: e.g. ibuprofen is almost completely removed similarly to other acid pharmaceuticals, whereas carbamazepine is generally removed by less than 50 %. Additional wastewater treatment processes such as polishing lagoons, infiltration and ozonation can improve the overall efficiency.

Kanda *et al.* (2003) found variances in different types of sewage treatment plants in the United Kingdom, influenced by the type of process used. The percentage efficacy of removal of PhAC and PCP by sewage treatment works ranges from 12 - 90%. Those sewage works that use activated sludge or oxidation ditches rather than biological filters or reed beds were more effective at removing the PhAC and PCP from the final ‘product’. Moreover sludge

retention times strongly influence the effectiveness. They found triclosan, an anti-microbial compound used in personal care products such as tooth paste, shower gels, hand wash in all crude and processed samples. This compound could be a risk because of its potential to raise bacteria resistance, but at low concentrations levels such effects are not expected.
Oxidation processes can be applied successfully for the removal of pharmaceuticals. The formation of by-products receives some attention, but their identity is still largely unknown.

7.2 DRINKING WATER PRODUCTION

A literature review on the removal of PhAC, PCP and EDCs in drinking water production was recently published by Snyder *et al.* (2003). Based upon literature reports with specific classes of compounds or compounds with similarities to other trace pollutants that have been studied in more detail, they anticipated the following performances for different unit processes:

- Activated carbon gave good (70 – 90 %) to excellent (> 90 %) results, especially for hydrophobic substances;
- Ozonation/advanced oxidation showed low (20 – 40%) to excellent (> 90 %) removal, specially for compounds with electron-activating functional groups (thiols, amines or hydroxyl) located near C=C bonds;
- UV: fair (40 - 70 %) to good (70 – 90 %);
- Cl_2/ClO_2: poor (< 20 %) to fair (40 – 70 %);
- Coagulation/flocculation: poor (< 20 %) to low (20 – 40 %);
- Softening/metal oxides: poor (< 20 %) to low (20 – 40 %);
- Nanofiltration: good (70 – 90 %) to excellent (> 90 %) depending on molecule size and polarity and membrane properties;
- Reverse osmosis: excellent (> 90 %).

Results of other studies on the removal of PhAC during drinking water treatment have been published by Janex-Habibi *et al.* (2003), Ternes *et al.* (2002), Heberer (2002), and Mons *et al.* (2003). The results of these studies are comparable to the overall results of the review prepared by Snyder *et al.* (2003).
Oxidation of pharmaceuticals during ozonation and advanced oxidation are promising processes for efficient removal of pharmaceuticals like bezafibrate, carbamazepine, diazepam, diclofenac, 17a-ethinylestradiol, ibuprofen, iopromide, sulfamethoxazole and roxithromycin in drinking water treatment (Huber *et al.,* 2003). The major ozonation by-products have even been identified for some compounds (Huber, 2003).
To be effective, UV doses used for treatment of micro pollutants must be several orders of magnitude higher than those used for disinfection (< 30 mJ/cm^2). Few data on PhAC removal during UV treatment exist, but at high UV doses of 3000 mJ/cm^2 the removal of some antibiotics ranged from 30 – 80 %. In combination with ozone or hydrogen peroxide UV may be practical in some situations. Oxidation of fragrances was achieved using UV in combination with hydrogen peroxide.

7.3 SUMMARY AND CONCLUSIONS

Since there is often no direct relation between sampling of influents and effluents of WWTPs the data for removal are not sufficiently accurate. It would be useful to draw up a mass balance between input, output, adsorption on sludge and degradation and evaporation to evaluate the relative contribution of the different mechanisms of removal and to make the next step to optimisation of process conditions.

Research on removal in drinking water production processes must be focussed on PhAC and PCP frequently found at low levels in drinking water, and at higher levels in surface water, to provide data that will avoid contamination of drinking water with PhAC and PCP.

8

GENERAL CONCLUSIONS

8.1 OVERALL SUMMARY

In the past 10-15 years much effort has been put into the assessment of pesticides in the (aquatic) environment. Experts confirmed that problems with pharmaceuticals might be of the same proportions and that similarities exist between the issue of pesticides and the issue of pharmaceuticals in the water cycle. Similar to pesticides pharmaceuticals also intend to affect organisms or biological processes, are present widely in the environment and consist of a wide range of chemical structures. Regarding to personal care products there are few data on occurrence and fate in the environment and removal during water treatment processes.

With regard to pharmaceuticals much research has been carried out on occurrence in wastewater and surface water. Most data from Western Europe and the U.S. Data on the occurrence of pharmaceuticals in groundwater and drinking water are more scarce.

Standardised analytical methods for detection of commonly occurring pharmaceuticals are critical. Further development is required to improve performance characteristics for a number of selected compounds. Matrix-effects are one of the difficulties to overcome in analyses.

Although information on the removal of pharmaceuticals in wastewater and drinking water treatment is becoming available, much is still unknown as to the fate of these contaminants in wastewater and drinking water production plants. Activated carbon, (advanced) oxidation processes and membrane filtration are showing promising results for efficient removal of many pharmaceuticals during drinking water production.

With regard to aquatic ecotoxicity, there is a significant lack of information. Data currently available show that chronic effects might occur at the concentrations detected in surface water.

As human pharmaceuticals are intended for human consumption, much data are available on human health effects. Comparison of the concentrations detected so far in drinking water with provisional safe levels, leads to the conclusion that human health effects are unlikely.

8.2 RESEARCH NEEDS

Based on the information currently available the next research needs can be defined as:

- Improvement of performance characteristics of analytical methods and implementation of validated analytical methods for monitoring.
- A better understanding is needed of removal processes in wastewater treatment and how to improve their efficiency in order to reduce emissions to the water environment.
- Monitoring programmes for groundwater and drinking water are needed for a better insight into the occurrence in these types of water.
- Possibilities for source control and source specific treatment should be investigated (e.g. separate treatment of wastewater from hospitals or after urine separation).

- More information is needed on the removal efficacy of pharmaceuticals during various drinking water treatment processes, including bank filtration, activated carbon filtration, ozonation, membrane filtration and Cl_2- and UV-disinfection;
- Data on the effects on ecosystems are largely lacking. For an ecotoxicological risk-assessment more information is needed.

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