Human pharmaceuticals in the water cycle

KWR 2013-062 | STOWA 2013-23

KWR
Watercycle Research Institute

stowa

Human pharmaceuticals in the water cycle

KWR
Watercycle Research Institute

KWR Nieuwegein
Groningenhaven 7
3433 PE Nieuwegein
0031 (0) 30 60 69 511
0031 (0) 30 60 61 165 (fax)
info@kwrwater.nl
www.kwrwater.nl

Mailing address
Post Box 1072
3430 BB Nieuwegein

stowa

STOWA
Stichting Toegepast Onderzoek Waterbeheer
Postbus 2180
3800 CD Amersfoort
T 0031 (0) 33 460 3200

Visiting address
Stationsplein 89, vierde etage
3818 LE Amersfoort
E-mail: stowa@stowa.nl
Internet: www.stowa.nl

ISBN 978.90.5773.622.3

COLOPHON

PUBLICATION Stichting Toegepast Onderzoek Waterbeheer
Postbus 2180
3800 CD Amersfoort

WRITTEN BY
Anja Derksen (for STOWA)
Thomas ter Laak (KWR)

SUPPORTED BY
Cindy de Jongh, Hans Huiting, Roberta Hofman-Caris (KWR)

SUPERVISED BY
Bert Palsma (STOWA)
Annemarie van Wezel (KWR)
Jan Hofman (KWR)
Harry Römgens (RIWA)
Andre Bannink (RIWA)
Peter Stoks (RIWA)

TRANSLATED BY
Jim Adams

COVER PHOTO © Ivar Pel Fotografie Utrecht

PRINT Kruyt Grafisch Adviesbureau

STOWA STOWA 2013-23
KWR KWR 2013-062

ISBN 978.90.5773.622.3

STOWA IN BRIEF

The Foundation for Applied Water Research (in short, STOWA) is a research platform for Dutch water controllers. STOWA participants are all ground and surface water managers in rural and urban areas, managers of domestic wastewater treatment installations and dam inspectors.

The water controllers avail themselves of STOWA's facilities for the realisation of all kinds of applied technological, scientific, administrative legal and social scientific research activities that may be of communal importance. Research programmes are developed based on requirement reports generated by the institute's participants. Research suggestions proposed by third parties such as knowledge institutes and consultants, are more than welcome. After having received such suggestions STOWA then consults its participants in order to verify the need for such proposed research.

STOWA does not conduct any research itself, instead it commissions specialised bodies to do the required research. All the studies are supervised by supervisory boards composed of staff from the various participating organisations and, where necessary, experts are brought in.

The money required for research, development, information and other services is raised by the various participating parties. At the moment, this amounts to an annual budget of some 6,5 million euro.

For telephone contact number is: +31 (0)33 - 460 32 00.
The postal address is: STOWA, P.O. Box 2180, 3800 CD Amersfoort.
E-mail: stowa@stowa.nl.
Website: www.stowa.nl.

KWR WATERCYCLE RESEARCH INSTITUTE IN BRIEF

Safe and clean water is a vital good. As an internationally renowned research institute, KWR contributes to making safe and clean water available through its applied scientific research into the water cycle.

“Bridging science to practice” – that is our mission at KWR. We build bridges between science, business and society. Our strength lies in our ability to transform scientific knowledge into practical applications that our clients can directly implement. Our shareholders are the ten Dutch water companies.

KWR has a lean staff of 175, of whom 130 are scientists specialised in a wide range of fields. They work within three Knowledge Groups: Water Systems and Technology, Water Quality and Health, and Knowledge Management, and are active in projects throughout the Netherlands and, increasingly, elsewhere in Europe as well. The list of our innovative research projects is long and varied, and addresses key questions like climate change and ecosystems, water treatment and purification techniques, drugs in sewage water, Legionella prevention, software development and the interlinking of knowledge networks. The Dutch and international water sectors are highly dynamic, and KWR is a constant and active player in both. The government of the Netherlands has designated the water sector as one of its nine priority “top sectors”. In the resulting knowledge agenda for the water technology actors, we are collaborating closely with other research institutes like STOWA, RIONED and Wetsus.

KWR’s research focuses on four themes: healthy, advanced, sustainable and efficient water. It is not only a matter of having healthy water flowing from our taps in our homes, but also of having safe water outdoors in which we can bathe. KWR stands for research that is innovative and practice-oriented, research that draws on the latest technologies from many fields, including physics, chemistry, ecology and nanotechnology. In the event of emergencies or disasters – such as the EHEC outbreak in Germany or the fire in Moerdijk in the Netherlands – KWR experts are quickly called on to conduct front-line research themselves or to support regional laboratories in efforts to determine the human and environmental risks involved.

The sustainability theme will continue to grow in importance in the years to come. KWR’s initiatives in this area include studying ways of making productive use of seawater, and of transforming wastewater treatment from an energy-consuming activity to one that actually produces energy. Efficiency is a key theme when it comes to water purification, water distribution and wastewater treatment – the ultimate goal being to contain costs for government, the public and industry.

HUMAN PHARMACEUTICALS IN THE WATER CYCLE

CONTENT

STOWA IN BRIEF
KWR WATERCYCLE RESEARCH INSTITUTE IN BRIEF

1 INTRODUCTION
- **1.1** Rationale and background 1
- **1.2** Objective 1
- **1.3** Reading guide 2

2 PHARMACEUTICALS IN THE WATER CYCLE
- **2.1** Regulating human pharmaceuticals 3
- **2.2** Sources and diffusion of pharmaceuticals in the water cycle 4

3 CONCENTRATIONS AND LOADS
- **3.1** Pharmaceuticals in the water cycle in the Netherlands 6
- **3.2** Pharmaceutical loads in the water cycle 8

4 REMOVAL IN WASTEWATER AND DRINKING WATER TREATMENT
- **4.1** Properties of pharmaceuticals 10
- **4.2** Removal in conventional wastewater treatment and additional treatment techniques 10
- **4.3** Removal in drinking water treatment 13

5 EFFECTS ON THE ENVIRONMENT
- **5.1** Chronic and specific effects 15
- **5.2** Effects of degradation products 16
- **5.3** Effects of mixtures 16
- **5.4** Targeted effect measurement in effluents and surface water 17
- **5.5** Assessments of presence in surface water 19

6		EFFECTS ON HUMANS	
	6.1	Risk assessment of exposure to pharmaceuticals in drinking water	20
	6.2	Procedure to determine the effects of mixtures	20
7		POSSIBLE TECHNICAL MEASURES	
	7.1	Costs of measures for (supplementary) WWTP treatment	22
	7.2	Cost of measures for (supplementary) drinking water treatment	23
8		SYNTHESIS	
	8.1	Summary	25
	8.2	Knowledge gaps	26
	8.3	Points of particular interest	27
	8.4	Recommendations	29
		LITERATURE	31
	ANNEX 1	A historical perspective on pharmaceuticals: From emerging substances to emission reduction measures	45
	ANNEX 2	Environmental assessment in the pharmaceutical approval process	47
	ANNEX 3	ATC main groups	48
	ANNEX 4	Monitoring results (ranges)	49
	ANNEX 5	Traditional safety factors in risk assessments provide insufficient protection from pharmaceuticals with specific effects	51
	ANNEX 6	Provisional standards and PNEC values for surface water	53
	ANNEX 7	Target values in drinking water and drinking water sources	56
	ANNEX 8	Calculating limit values in drinking water and drinking water sources	57
	ANNEX 9	Preferred techniques for the removal of pharmaceuticals at WWTPs (Grontmij 2011)	59

1

INTRODUCTION

1.1 RATIONALE AND BACKGROUND

The objectives of the Administrative Agreement on Water (Ministerie van Infrastructuur en Milieu, 2011) include a more efficient management of the water cycle and significant cost-savings. In response, RIWA, KWR and STOWA engaged in strategic consultations aimed at pooling their knowledge and capabilities in the wastewater and drinking water cycles, to further develop their joint interests and, ultimately, to reduce the load of micropollutants in surface water.

Within the framework of this knowledge pooling effort, this report presents a collection of the research results on the issue of pharmaceuticals in the water cycle. The presence of pharmaceuticals in the environment has long been the focus of attention. The subject has gone through various stages, from the initial signalling of a possible new problem substance, to calling the attention of the stakeholders and further filling of knowledge gaps, to drafting policies for reducing emissions. This historical course is detailed in Annex 1.

In 2001, the Health Council already called for legislative attention to the issue of pharmaceuticals in the environment because “the risks cannot simply be brushed aside in advance as insignificant” (Gezondheidsraad, 2001). In a Policy Letter to the Lower House (Tweede Kamer, 2007) a number of actions were put forward with the aim of reducing emissions and filling knowledge gaps. In 2009 the Lower House was informed of their progress (Tweede Kamer, 2009). In the second half of 2012 this will happen again. Concurrently, pharmaceuticals also received increasing attention within the European Water Framework Directive (WFD): in its most recent revision of its priority substances list a recommendation is made to add a pharmaceutical, namely, the anti-inflammatory drug diclofenac, and the contraceptive pill’s active ingredient (ethinyloestradiol) (European Commission, 2012).

1.2 OBJECTIVE

There is a great deal of knowledge concerning the presence of and the potential risks associated with pharmaceuticals in the water cycle. However, in the case of the Netherlands, this knowledge is scattered in a broad range of reports and publications by different parties, such as STOWA, RIWA, the Directorate for Public Works and Water Management (Rijkswaterstaat), the drinking water companies and research institutions like KWR, RIVM, IVM and Alterra. A lot of knowledge is also available from international research and scientific literature.

The objective of this “Human pharmaceuticals in the water cycle: state-of-the-science” document is to provide, in a single report, a brief and concise summary of existing knowledge on the presence and the effects of pharmaceuticals in the water cycle, and on possible technical measures to reduce them. It is important to realise that directing attention to

pharmaceuticals in water touches on two concerns: having surface water of good quality, which is an ecological concern, and having clean sources for the production of drinking water, which is a public health concern.

Our focus is limited to human pharmaceuticals, including X-ray contrast media. We have chosen not to address veterinary pharmaceuticals: the path of these substances to the water environment, via manure application, leaching and runoff, is indirect and thus offers fewer means for reducing emissions (Montforts 2006; Kools 2008).[1] But this does not mean that veterinary pharmaceuticals (in another framework) would not merit attention.

Pharmaceuticals that target the hormone system, such as ethinyloestradiol, the active ingredient in the contraceptive pill, are also part of the study. However, the subject of hormone disruption is not dealt with explicitly: it is such a vast subject that it requires a separate study.

1.3 READING GUIDE

This report offers an overview of research work on human pharmaceuticals in the water cycle. It begins by discussing the legislative frameworks, the behaviour and presence of these substances in the water cycle, and their removal in wastewater and drinking water treatment. It then addresses the pharmaceuticals' effects on humans and the environment. This is followed by a discussion of emission reduction measures. Lastly, it provides a summary of the current state-of-the-science, knowledge gaps and points of particular interest, and ends with recommendations.

1 One exception is in this regard refers to the trend to process manure in manure processing installations. These produce an effluent stream that is treated in WWTPs. Veterinary pharmaceuticals that end up in the water system via this route raise the same issues as do human pharmaceuticals that enter the water systems via a WWTP.

2

PHARMACEUTICALS IN THE WATER CYCLE

2.1 REGULATING HUMAN PHARMACEUTICALS

A pharmaceutical consists of an active ingredient and different excipients. An active ingredient can be marketed in various formulations and under different brand names.

European legislation – Directive 2001/83/EC (EC, 2001), modified in Directive 2004/27/ EC (EC, 2004) – establishes that only registered and approved pharmaceuticals may be used. This registration can be carried out centrally at the European Medicines Agency (EMA), for the whole of Europe, or for each country separately. In the Netherlands, it is the Medicines Evaluation Board (CBG) that is responsible for the group of pharmaceuticals available (www.cbgmeb.nl).

The registration procedure for a human pharmaceutical requires that an environmental assessment be carried out (Annex 2). The environmental risk, however, cannot constitute grounds for the refusal of a substance's approval, because of the major importance of pharmaceuticals to public health. Nor is there any obligation to monitor a substance in the environment after it has received approval (Montforts et al., 2006). In contrast to human pharmaceuticals, the associated environmental risks can affect the approval of veterinary pharmaceuticals (www.cbgmeb.nl). There has been a call to make the information from a pharmaceutical's environmental assessment public upon its registration (Montforts & Keessen, 2008). Although EMA and CBG have expressed their commitment to this, no environmental information has been made public to date (van der Aa et al., 2011c).

Active ingredients can be classified in a number of ways. Common classification systems are based on the human body's organ system, the pharmaceutical's chemical structure, therapeutic mode of action, origin, route of administration and form of administration. A classification system that is very frequently used internationally is the ATC (Anatomical Therapeutic Chemical) code. The ATC code is made up of seven letters and digits, and refers to a specific active ingredient. The code's first letter indicates the pharmaceutical's main group (Annex 3). However, for research into the presence and behaviour of pharmaceuticals in the water cycle it is more pertinent to classify the substances on the basis of their use, persistence and physical-chemical properties (de Voogt et al., 2009; ter Laak et al., 2011a).

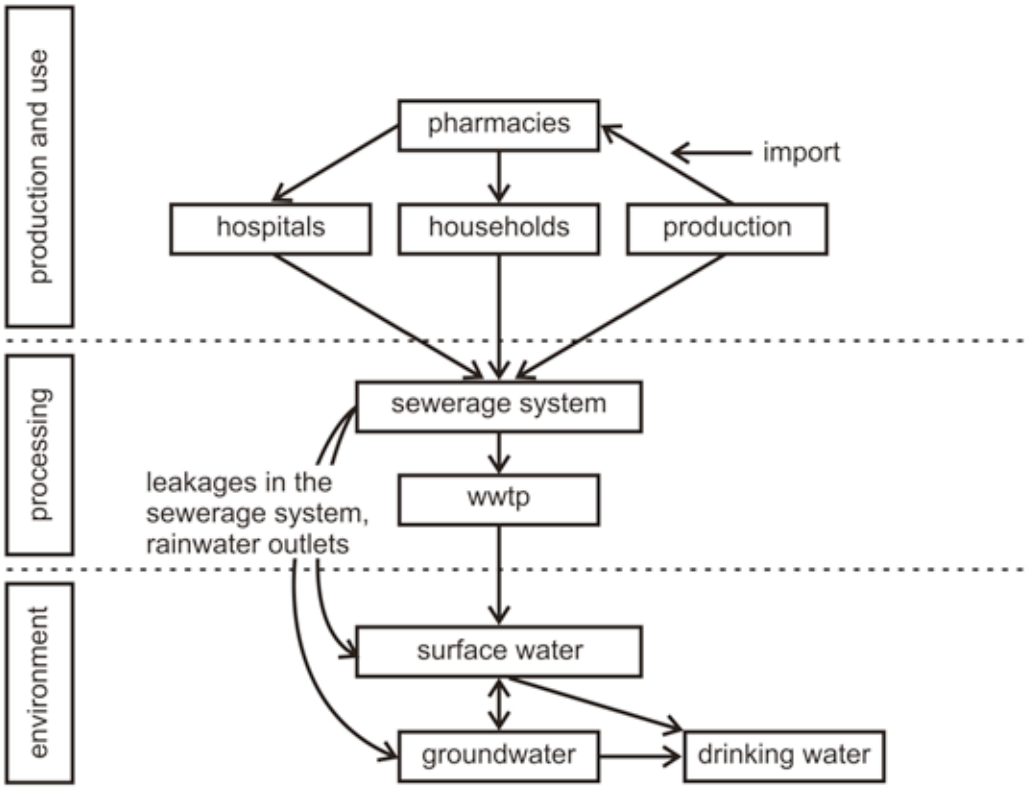
The use of human pharmaceuticals in the Netherlands is relatively low compared to that of other European countries (van der Aa et al., 2008). However, forecasts for the long term predict an increase of use due to the effects of an aging population and the medicalisation of society. Over the next forty years a 37% increase is expected in the Netherlands (van der Aa et al., 2011b).

2.2 SOURCES AND DIFFUSION OF PHARMACEUTICALS IN THE WATER CYCLE

Human pharmaceuticals can reach the water cycle through a variety of routes (see Figure 1). They can do so after being placed in dump sites, as residuals from industrial manufacture or as unused pharmaceuticals, and then leach into the groundwater. It is also possible that the effluent from the manufacture of pharmaceuticals occasionally or continuously contain pharmaceutical residues. They can then end up in the surface water via the treatment process (Larsson et al., 2007). For the most part, however, the pharmaceuticals are consumed. Used pharmaceuticals (and their metabolites) are excreted via urine (about 80%) and faeces (20%), and reach the wastewater treatment plant (WWTP) together with the rest of domestic wastewater via a sewerage system. The treated wastewater is then discharged into the surface water. In the case of sewerage systems that transport rainwater as well as domestic wastewater (combined sewerage systems), transport peaks can occur during heavy rainfall whereby some of the wastewater cannot be processed through the sewerage system. This wastewater is discharged, untreated via a so-called overflow into the surface water.

Pharmaceuticals can also end up in the groundwater because of (artificial) infiltration or leakages in the sewerage lines. Drinking water in the Netherlands is produced from surface water (37%), groundwater (58%) and bank filtration (6%) (Geudens, 2012). As mentioned above, pharmaceuticals occur primarily in surface water. Bank filtration water and groundwater can also contain residues of pharmaceuticals, but concentrations in bank-filtration water are usually lower than they are in surface water because the water's soil passage removes part of the substances, equalises the pollution peaks and dilutes the water with "clean" groundwater.

FIGURE 1 THE MATERIAL FLOW OF HUMAN PHARMACEUTICALS IN THE WATER CYCLE. SOURCE: ICBR (2010)



The concentrations of pharmaceuticals in the different parts of the water cycle depend on:

1 the sale of pharmaceuticals,
2 the proportion of the sold pharmaceuticals that is actually used,
3 the proportion of the dose that the user excretes and what metabolites are formed in the process,
4 the proportion that passes through the wastewater treatment and what degradation products are formed in the process,
5 the proportion in the surface water that is adsorbed to sediment or is broken down, and what degradation products are formed in the process,
6 the degree to which these substances pass through the soil, for example, when surface water is infiltrated for drinking water production,
7 the degree to which they are removed during drinking water production processes.

3

CONCENTRATIONS AND LOADS

3.1 PHARMACEUTICALS IN THE WATER CYCLE IN THE NETHERLANDS

Approximately 850 pharmaceuticals (i.e., active ingredients) are used in the Netherlands (RIZA/RIWA, 2001). Of these, about 200 have been measured in the environment worldwide (Roig, 2010; Verlicchi et al., 2012). A portion of these are regularly found in the water cycle.

Most measurements of pharmaceuticals are made in surface water and wastewater, but measurements are also regularly made in groundwater and drinking water (Kümmerer, 2008). The overview presented below shows the periodicity of measurement activity in the Dutch water cycle and the databases in which the data produced are stored.

1 The RIWA database contains in principle four-weekly measurement data from surface water in the Rhine and Meuse basin. The Dutch sampling locations are: Lobith, Nieuwegein, Nieuwersluis and Andijk for the Rhine, and Eijsden, Heel, Brakel, Keizersveer/Gat van Kerksloot for the Meuse. In addition, at Stellendam/Scheelhoek a mixture of 25% Meuse water and 75% Rhine water is sampled. The database also includes results from associated companies in the basin areas in Germany, Switzerland and Belgium. Depending on the location in the Netherlands, up to 67 pharmaceuticals and up to 10 X-ray contrast media have been measured in the Rhine (ter Laak et al., 2010; RIWA, 2011a), and a maximum of 68 pharmaceuticals and 9 X-ray contrast media in the Meuse (www.riwamaas.org).

2 The REWAB database of the Dutch drinking water companies contains measurement data from drinking water sources and from purified water. A total of 54 pharmaceuticals are measured. However, the number of substances varies significantly by water type and location because measuring for these substances is not pertinent for every source; moreover, there is no obligation to report on these substances.

3 The RWS Waterdienst database contains 33 pharmaceuticals, which are measured twice a year at 13 locations in the Dutch National Waters (Kotte, 2009; ter Laak et al., 2011b).

4 WATSON database wastewater

This database contains monitoring data on 513 substances in wastewater (influent and effluent), including 42 pharmaceuticals and 6 X-ray contrast media (Grontmij, 2011b). The database was originally set up by Rijkswaterstaat with data from national screening research, which were subsequently supplemented with recent and less recent screenings by 12 waterboards (STOWA 2009d). In 2012 the database is to be further expanded with recent monitoring data, which include various pharmaceuticals that have hitherto not been entered into the database. The database is currently managed by Deltares and provides the statistical basis for the Pollutant Release and Transfer Register (www.emissieregistratie.nl). The data are public and are supplied upon request, but the locations remain anonymous.

5 CIW database surface water

The CIW database contains monitoring data for a large number of substances in surface water, including pharmaceuticals. The data originate from the waterboards' operational monitoring programmes for about 3,000 monitoring locations. In addition some, but not

all, waterboards also provide data from project-specific research work. Starting this year, the monitoring data will also be recorded by Rijkswaterstaat. The database is managed by the Informatiehuis Water. Monitoring data are supplied upon request.

A more detailed overview of the range of measurements and databases is provided in Annex 4.

Wastewater and smaller bodies of surface water are not the object of regular measurements for pharmaceuticals. The waterboards and/or STOWA have, however, conducted measurements with some regularity over the past few years on a project basis (STOWA, 2011a,b,c; 2010; 2009a, b, c, d; 2008; 2007b, c; 2006; Grontmij|AquaSense, 2007; 2008; 2009; den Elzen & Malsch, 2009; Mill et al., 2006; Marsman et al., 2009). Furthermore, measurements are also conducted by research institutes and universities on a project basis (Mons et al., 2003; Schrap et al., 2003; Versteegh et al., 2003; Versteegh et al., 2007; De Jongh et al., 2012; ter Laak and Hofman, in prep.; RIZA, 2006a, b; Sacher & Stoks, 2003).

The measurement limits for these substances can vary according to the substance and matrix involved. For most pharmaceuticals the measurement limit in water is 0.01 µg/L, but this limit can be higher for some substances and for more complex matrices, such as wastewater. Concentrations of pharmaceuticals are usually highest in (untreated) wastewater and, through degradation, sorption (binding) and dilution, become lower through the course of the water cycle.

Untreated wastewater regularly contains more than one hundred micrograms of pharmaceuticals and degradation products per litre (Oosterhuis et al., 2011; Verlicchi et al., 2012). Concentrations of individual substances vary significantly, depending on human consumption and metabolism, removal during treatment and dilution, degradation and sorption in the environment. Surface water systems that are heavily loaded with WWTP effluent can, particularly when drainage levels are low, contain tens of µg/L of pharmaceuticals and degradation products (STOWA 2011a; ter Laak and Hofman, in prep.). The total concentrations found in the Rhine and Meuse usually amount to several µg/L (RIWA, 2011b, a; ter Laak and Hofman, in prep.). Recent research has demonstrated that metformin and its degradation product guanylurea constitute more than half the total pharmaceutical concentrations (Scheurer et al., 2009; Oosterhuis et al., 2011; RIWA, 2011a; Trautwein and Kümmerer, 2011; STOWA 2011c; Scheurer et al., 2012; ter Laak and Hofman, in prep.). X-ray contrast media, in turn, make up tens of percentage shares in the total concentrations, while beta-blockers, painkillers, antiepileptics and antibiotics each account for a few percentage shares.

Total concentrations of pharmaceuticals and degradation products in (artificially) soil-filtered water, seepage water and bank-filtration water fall below the µg/L level (Reddersen et al., 2002; De Jongh et al., 2012). Also, the range of pharmaceuticals depends on the local hydrology, sorption and degradation in the soil, and can be a reflection of historical pollution. Thus, for instance, phenazone is regularly found in bank-filtration water (ter Laak et al., 2012), while this painkiller is no longer sold in Europe and is only found rarely or in low concentrations in surface water (RIWA, 2011a; De Jongh et al., 2012). No pharmaceuticals are found in drinking water produced from deep and old groundwater. But drinking water produced from surface water, bank-filtration water and vulnerable groundwater sources can sometimes contain traces of pharmaceuticals (Mons et al., 2003; Versteegh et al., 2003; Versteegh et al., 2007; De Jongh et al., 2012). This usually involves a few substances and concentrations at the ng/L level.

Concentrations can however vary significantly with time and place. Concentrations in WWTP effluent and surface water are strongly dependent, among other things, on the input, the transformation processes and dilution (Ort et al., 2010). This should be taken into account during monitoring. In order to determine the average concentration levels and loads on the basis of measurement data, time-integrated samples have to be taken. This is much less pertinent for bank-filtration water and groundwater, because the underground aquifers maintain stable temperatures and time variations are equalised due to long residence times and mixing.

3.2 PHARMACEUTICAL LOADS IN THE WATER CYCLE

It is important, when establishing emission reduction measures, to have insight into the load of pharmaceuticals within the entire water cycle. This knowledge gap has, over the past few years, been steadily filled. Researchers have studied the contribution of residential areas, hospitals and various healthcare institutions to the total pharmaceutical load in the water cycle. Calculations and measurements for healthcare institutions and households have supplied emission data (STOWA, 2011b; STOWA, 2009a). These data allow for calculations to be made of the load on WWTPs and the contribution of the different sources. These emission data show that loads from hospitals usually account for <10% of the total pharmaceutical load (excluding X-ray contrast media) on WWTPs (STOWA, 2009a; STOWA 2011a; ter Laak and Hofman, in prep.). The contributions of other healthcare institutions is a lot lower, typically 15% (STOWA, 2011b). The contribution can therefore vary significantly per pharmaceutical and is strongly dependent on the local situation. At the local level, the contribution to the load on a WWTP of a hospital or healthcare institution can in fact be substantial. Research has also studied the contribution of overflow, which is directly discharged into surface water. This contribution is estimated to be less than 1% of the load that reaches a WWTP (Grontmij, 2011a). Since this water is not subjected to any treatment, this route is of relevance to small receiving water bodies. The contribution to the total load on surface water is estimated, for individual substances, to be 1-10% (ICBR, 2010).

Not much research has yet been carried out on emissions of pharmaceuticals via dump sites or manufacturing locations. But there is a consensus in Europe that this type of diffusion is relatively insignificant (Kümmerer, 2008). Research by Blom et al. (1995) shows that, in the Netherlands, 8.3% of prescribed prescription pharmaceuticals are not used. For the most part these are returned to the pharmacy or are collected as small chemical waste and incinerated at high temperatures. A smaller proportion ends up in the sewerage or is carried off with household rubbish. Over the last few decades household rubbish in the Netherlands has been incinerated, so that the pharmaceuticals it might contain have not ended up in the environment. Therefore it is only the old dump sites that are possible point sources for pharmaceuticals in the environment (ter Laak et al., 2012). The experience of batch production of pharmaceuticals shows that approximately 0.2% of the active ingredient is discharged in the flushing water for every batch (Oranjewoud, 1999). Moreover, many generic pharmaceuticals are manufactured outside Europe. Studies have demonstrated, however, that the pharmaceutical industry's waste streams in India can be enormous (Larsson et al., 2007) and can present big ecological and human risks at a local level.

By far the greatest part of human pharmaceuticals therefore end up in surface water via WWTPs (Kümmerer, 2008). Every year in the Netherlands at least 11 tons of pharmaceuticals (excluding X-ray contrast media) are discharged into surface water via WWTP effluent

(Grontmij, 2011a). The load at the WWTPs appears for the most part to originate in residential areas (STOWA, 2011a; STOWA 2011b; STOWA, 2009a; ter Laak and Hofman, in prep.). Some substances are prominent, namely, X-ray contrast media and metformin, an antidiabetic that has recently been added to the analysis programme. Both medications are consumed in high daily dosages. Guanylurea, the metformin degradation product, is also prominent.

The water cycle in the Netherlands also receives considerable loads from abroad. About 46 million people live in the Rhine basin – upstream from Lobith – , while in the Meuse basin – upstream from Eijsden – there are about 5.3 million people (RIWA, 2009). Calculations based on RWS and RIWA data indicate that at least 100 tons of pharmaceuticals flow annually into the Netherlands via the large rivers and flow out into the North Sea (Walraven and Laane, 2009; ter Laak et al., 2010). In these studies, X-ray contrast media account for approximately two-thirds of the load (metformin and guanylurea were not studied). More than half of the pharmaceutical load in Dutch surface water comes from abroad. The annual pharmaceutical load moreover seems to be quite predictable on the basis of pharmaceutical use in a river's basin, the human excretion of pharmaceuticals and their removal in WWTPs. Loads and concentrations can however show significant short-term variations because of variations in use, WWTP removal efficiency, degradation in surface water, as well as changes in surface water discharge (ter Laak et al., 2010).

One must however take due caution when interpreting and comparing the calculations of the loads from healthcare institutions, residential areas and abroad. This, because the analysis programmes differ, only a limited number of pharmaceuticals are usually measured, the measurements are conducted in different years and under different (hydrological) circumstances, all of which makes the comparison of the figures problematic. But the calculations can be used as rough indicators, and for the determination of emission routes for a specific area. The latter has been done in area studies in Utrecht (STOWA, 2011a) and Limburg (ter Laak and Hofman, in prep.). By combining the calculated emission with the information on the area's WWTPs and receiving surface water, the hotspots can be determined and target measures elaborated.

4

REMOVAL IN WASTEWATER AND DRINKING WATER TREATMENT

4.1 PROPERTIES OF PHARMACEUTICALS

The physical-chemical properties of a substance is decisive for its behaviour in the water cycle. The physical-chemical properties of pharmaceuticals vary considerably. They are generally organic substances, ranging from small, simple substances to large, complex ones. Most pharmaceuticals are polar (soluble in water), although some substances are relatively non-polar (soluble in fat). They are moreover made up of a wide spectrum of active groups, so that in water they can be neutral, positively charged, negatively charged, or even have two opposite charges in different positions in a molecule (Kümmerer, 2008). This wide spectrum of properties means that their behaviour in the water cycle can vary considerably.

Nonetheless they do have a few generic properties. They are for the most part not volatile and quite stable because, after being consumed, they have to remain intact in order to disperse in the body and have their intended effect. They are also biologically active, which is to say that they are designed, at low dosages, to have a specific effect on a biological system. These properties mean that pharmaceuticals can be mobile and persistent in the water cycle and can, in low concentrations, have an effect on biological systems. This is why their presence in the water cycle might present risks and requires attention.

4.2 REMOVAL IN CONVENTIONAL WASTEWATER TREATMENT AND ADDITIONAL TREATMENT TECHNIQUES

For decades now, the waterboards, STOWA and Rijkswaterstaat have conducted a great deal of research into the removal of organic micropollutants from wastewater. Apart from conventional biological wastewater treatment, other types of treatment (e.g., membrane reactors and the 1-STEP filter) as well as additional treatment techniques (e.g., sand filtration, activated carbon filtration and advanced oxidation) have received attention.

Without extra measures, conventional biological wastewater treatment removes about 65% of the total pharmaceutical load in the influent. This percentage is based on pharmaceutical content measurements above the WWTP influent and effluent reporting limits (excluding X-ray contrast media and antidiabetics) (STOWA, 2011c). The removal rates can however vary significantly per substance, from practically zero removal to complete removal (see Figure 2). Large variations in removal percentages can also occur within substance groups (Verlicchi et al., 2012). Moreover, substances that are excreted in conjugated form return to their precursor form if the conjugation is undone during the wastewater treatment.[2]

2 Conjugation is part of human metabolism and makes it possible for the pharmaceutical to be joined to a bodily substance (e.g., gluconoride) to make it more soluble and easier to excrete.

The purification efficiency attained in conventional activated sludge systems varies, but the causes for this have not been studied sufficiently. It appears that those conditions that are favourable for good nitrification – i.e., sludge retention times exceeding 10 days at 10°C – are also favourable for the removal of pharmaceuticals (Clara et al., 2005). Those substances that bind well to the activated sludge are removed effectively. This mainly concerns the more non-polar substances, such as ethinyloestradiol, the active ingredient in the contraceptive pill (STOWA, 2011C). However, the removal of most pharmaceuticals through sorption to activated sludge in conventional WWTPs is marginal (Jelic et al., 2012).

A number of research projects have focused on other, or supplementary,[3] treatment techniques, with the aim of radically improving the efficiency in the removal of micropollutants, including pharmaceuticals. In the Netherlands, this includes research into: a membrane bioreactor (MBR) (STOWA, 2006), a 1STEP filter (STOWA, 2009c), activated carbon filtration (STOWA, 2010b) and various oxidation techniques combined with activated carbon (STOWA, 2009b). Research has also been carried out at various locations elsewhere in Europe. In Spain, the removal of pharmaceuticals by conventional treatment processes and by MBRs has been compared (Radjenovic et al., 2007; Radjenovic et al., 2008; Petrovic et al., 2009; Radjenovic et al., 2009). Large-scale research projects have been undertaken in Switzerland (EAWAG)[4] and Germany[5] in particular. These involve studying the removal of pharmaceuticals (and other micropollutants) through conventional activated sludge systems, MBRs, ozone treatment and other advanced oxidation processes, the application of activated carbon, and various filtration techniques. In Switzerland, this led to plans for the broad introduction of extra treatment steps in the country's WWTPs.

Over the past few years more and more attention has also been directed to degradation products, including those of pharmaceuticals (Escher and Fenner, 2011). Ternes (2012) shows that today's biological water treatment does not result in the complete removal of substances, but that it produces a broad range of degradation products. A number of these degradation products are (much) more stable and might be more toxic than the precursors, and some of them are found in drinking water.

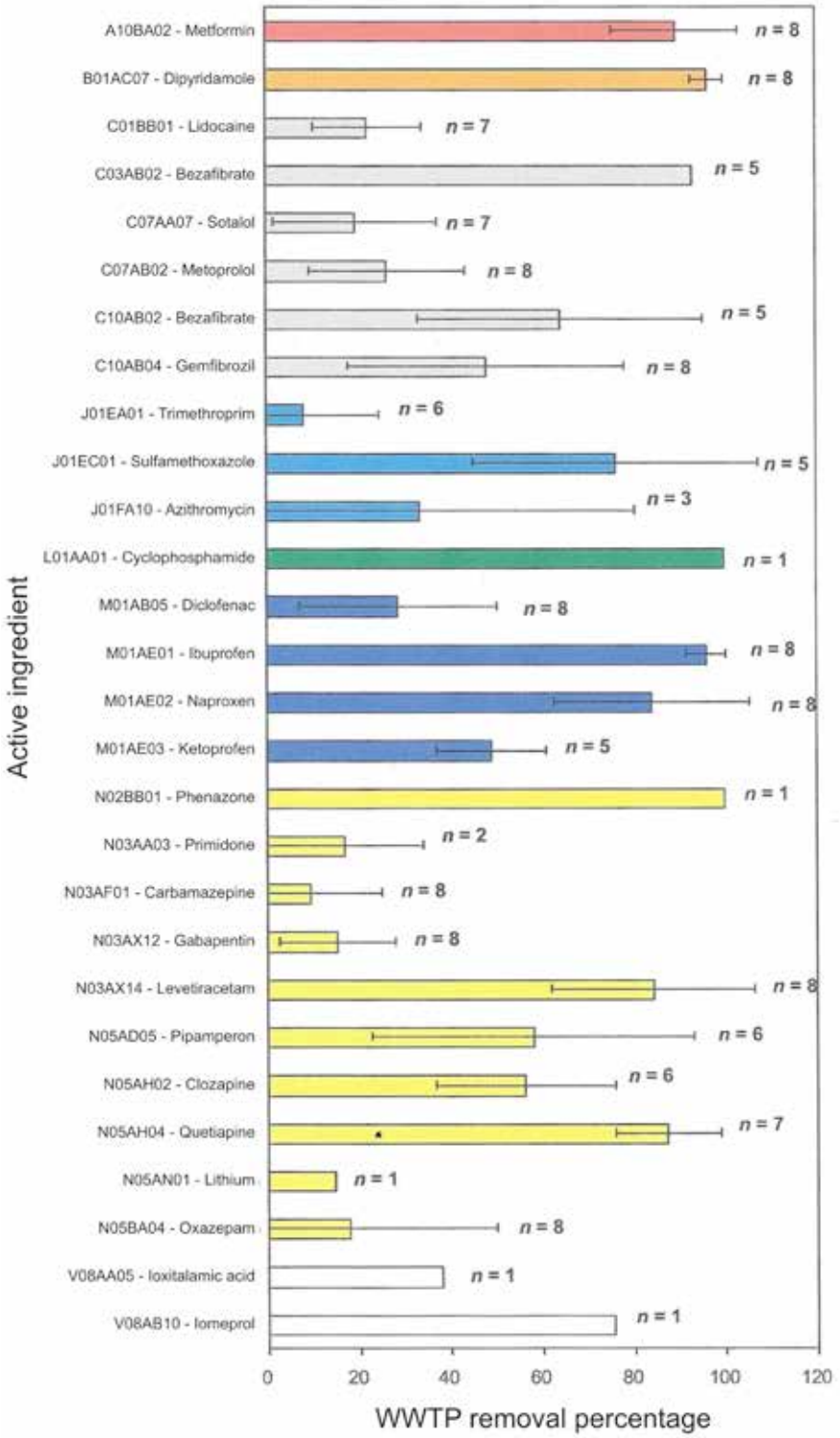
On the basis of this research, Grontmij (2011a) conclude that the best results are achieved by using a combination of an oxidation technique (e.g., ozone treatment) and an adsorption technique (e.g., activated carbon filtration). An optimal application of the two techniques results in an average removal rate of 90% of practically all pharmaceuticals. It is also possible to only use an activated carbon filter. The removal rate of activated carbon is 70%, but polar substances, in particular, are not removed as effectively. Moreover, the removal efficiency of these filters decreases with long-term use, so that the costs of filter regeneration or replacement have to be considered in light of the decreased removal efficiency.

3 These are supplementary treatment processes that are installed – as integrated or stand-alone systems – at the end of the conventional biological wastewater treatment system.

4 "MicroPoll" project, http://www.bafu.admin.ch/; themes: water protection, micropollutants.

5 Milieuministerie NordrheinWestfalen (MKULNV) project: "Elimination von Arzneimitteln und organischen Spurenstoffen," www.micropollutants.net (12 sub-projects, various techniques, including full-scale, metabolite formation with ozone).

FIGURE 2 **AVERAGE REMOVAL PERCENTAGES BASED ON MEASUREMENTS TAKEN AT 8 WWTPS. FOR EACH SUBSTANCE, AN INDICATION IS GIVEN OF THE NUMBER OF MEASUREMENTS (N) THE AVERAGE IS BASED ON, AS WELL AS THE STATISTICAL DISPERSION (STANDARD DEVIATION). LITHIUM AND IODINATED X-RAY CONTRAST MEDIA WERE ONLY MEASURED ONCE. SOURCE: STOWA (2011C).**

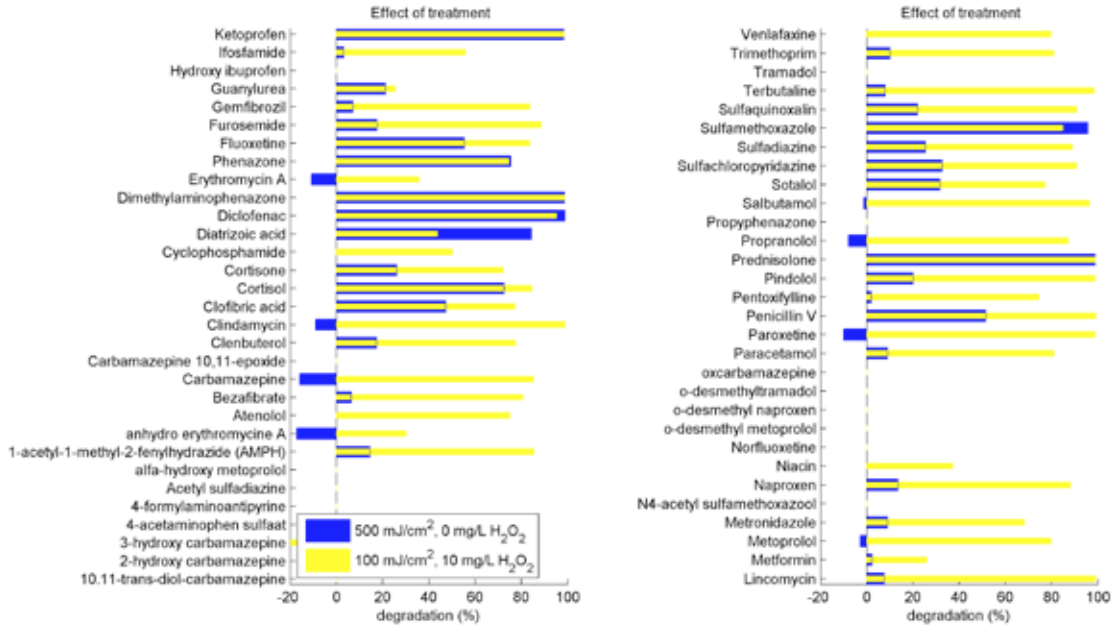


4.3 REMOVAL IN DRINKING WATER TREATMENT

Since the detection of the herbicide bentazon in drinking water in the late 1980s, the drinking water companies and KWR have conducted a great deal of research into the removal of organic micropollutants. This has involved much work on advanced treatment techniques such as ozone, UV disinfection and oxidation, activated carbon filtration and membrane filtration. The efforts have ultimately led to the large-scale application of activated carbon in bank water extraction along the Lek river, and the application of ozone and activated carbon and, later, UV disinfection and UV peroxide treatment, to surface water. In addition, the scope of the research into pesticides has been broadened to encompass all sorts of micropollutants, including pharmaceuticals.

Pharmaceuticals are frequently relatively small and charged compounds which are quite water-soluble. This means that they are difficult to remove from water. The research indicates that activated carbon treatment – which is often an important treatment step – is actually less suitable for the adsorption of such compounds from water. Activated carbon is suited primarily for the adsorption of relatively non-polar molecules. Moreover, the competition with natural organic material plays a big role in activated carbon adsorption. The larger, negatively charged molecules are generally best filtered using nanofiltration and reverse osmosis.

FIGURE 3 REMOVAL OF PHARMACEUTICALS BY UV PEROXIDE TREATMENT. SOURCE: HOFMAN-CARIS ET AL (2012)



The pharmaceutical removal efficiencies of different (advanced) treatment techniques has been studied on a pilot scale. The research concerned the removal of a wide range of pharmaceuticals using existing (activated carbon) and new (affinity sorption) sorption techniques (Bauerlein et al., 2012b; de Graaff et al., 2011; Bauerlein et al., 2012a). It also examined the extent to which nanofiltration membranes can filter pharmaceuticals (Verliefde, 2008) and which pharmaceuticals are transformed by oxidation techniques such as UV/peroxide oxidation (HofmanCaris and Beerendonk, 2011; HofmanCaris et al., 2011; Wols and HofmanCaris, 2012). These studies purposefully selected a set of a few tens of pharmaceuticals with a wide range of physical-chemical properties (ter Laak et al., 2011). This set of pharmaceuticals makes it possible, using statistical models, to relate a treatment

technique's contribution to the removal to the properties of the substances (Wols and Vries, 2011). These models are called QSARS (Quantitative Structure Activity Relationships), and can be used to predict the removal of other substances on the basis of their physical-chemical properties and the treatment technique involved. The efficiency of these techniques varies depending on the substance (see Figure 3 for the example of UV peroxide treatment). Removal rates using activated carbon are >80% for most substances. But very polar and charged substances – including some pharmaceuticals – are removed less effectively with this technique. Oxidation techniques, such as UV/peroxide, with the right dose, result in removal rates of >70% for most pharmaceuticals. However, some substances show much worse removal rates. The removal efficiency of nanofiltration is estimated to be 75%-85%; but this technique's removal rates are lower for small, neutral organic molecules.

5

EFFECTS ON THE ENVIRONMENT

5.1 CHRONIC AND SPECIFIC EFFECTS

Although knowledge about the effects of pharmaceuticals is increasing rapidly, there is still much that is unknown. The concentrations in surface water are typically much lower than the concentrations that, under laboratory conditions, have short-term, measurable effects on organisms (Fent et al., 2006; Cunningham et al., 2006; Webb, 2001; AquaSense, 2003). Organisms in the environment however are subject to long-term exposure to a cocktail of pharmaceuticals (and other substances). The long-term and combination effects are thus also important for risk assessment. Furthermore, pharmaceuticals are designed to be biologically active and can, compared to "normal" substances, present completely different mechanisms of action. These effects are not always measurable using standard biological measurement methods. The biological systems upon which the pharmaceuticals act are not unique to humans: they are also present in fish, crustaceans and other aquatic organisms. Therefore, in aquatic organisms specific effects can be expected that are related to the mechanisms of action of the pharmaceuticals. There are also examples of pharmaceuticals that have unexpected effects.

In the process of assessing a substance's risk, safety factors are frequently applied to correct for uncertainties associated, for instance, to the transposition from laboratory to the field and to differences between species. For specific active substances, such as pharmaceuticals or hormones, these correction factors do not always provide sufficient protection (Boxall et al., 2008, Ankley et al., 2005, Cunningham et al., 2006). Annex 5 presents a few examples.

Another element that needs to be taken into account is the fact that some pharmaceuticals appear to have unusual dose-effect relationships. Effects can be observed at very low concentrations (ng/L), but disappear at higher concentrations (Guler & Ford, 2010; de Lange et al., 2006). One example is the effect of fluoxetine and ibuprofen on the activity of crustaceans at concentrations of 10100 ng/L (de Lange et al., 2006).

Examples of specific effects and unexpected effects include:[6]

- High sensitivity of algae and blue-algae to antibiotics (Webb, 2001; RIWA/RIZA,
- 2001; AquaSense, 2003; HallingSørensen, 2000; Holten Lützhøft et al., 1999),
- High sensitivity of algae to beta-blockers (Escher et al., 2005; Escher et al., 2006),
- Kidney damage due to diclofenac (Green et al., 2006; Hoeger et al., 2005; Mehinto et al., 2010; Schwaiger et al., 2004; Triebskorn et al., 2004; Triebskorn et al., 2007),
- Disturbance of sexual behaviour (Sebire et al., 2008),
- Massive release of mussel oocytes and spermatozoa (spawning) due to fluoxetine
- (Fong, 1998; Fong et al., 1998; Fong et al., 2001),
- Disturbance of feeding activity (de Lange et al., 2006; Quinn et al., 2009; Nassaf et al.,

6 Apart from the effects mentioned, the use of antibiotics can also lead to the development of resistances so that there is a risk that illnesses cannot be treated as effectively. This subject however is beyond the range of this report.

- 2010; Stanley et al., 2007; Berninger et al., 2011),
- Disturbance of swimming behaviour (Guler & Ford, 2010; Painter et al., 2009; Nassef et al., 2010),
- Disturbance of crustacean moulting (Dietrich et al., 2010a),
- Effects on immune system (Gagné et al., 2006).

An important conclusion is that, when specific effects are included in the risk assessment of pharmaceuticals, the effects at environmental concentrations are real.

5.2 EFFECTS OF DEGRADATION PRODUCTS

Apart from the active ingredients themselves, it is desirable that their degradation products also receive attention. Degradation products can arise from:

1 human metabolism,
2 degradation in the WWTP,
3 degradation in the environment caused, among others, by bacteria under the exposure to light, and
4 in the drinking water treatment process (Ternes, 2012).

Metabolites or degradation products are sometimes much more stable than their precursors. For this reason analyses and effect measurements need also to target these metabolites and degradation products. One example is the benzodiazepine group (tranquilizers), which are quickly metabolised in the body into the much more stable oxazepam (Besse & Garric, 2007).

A number of degradation products seem to occur in very high concentrations. In the area study on pharmaceuticals in Limburg (ter Laak and Hofman, in prep.) three metabolites were found among the top ten loads: hydroxy ibuprofen, 10, 11-trans-diol carbamazepine and guanylurea. Guanylurea is the degradation product of the antidiabetic metformin, which under aerobic conditions is not broken down further by bacteria or through exposure to light (Trautwein and Kümmerer, 2011). Very stable degradation products are also formed from iodinated X-ray contrast media and from the antiepileptic carbamazepine (Schulz et al., 2008; Kormos et al., 2010; Pérez et al., 2007).

In most cases, the metabolites and degradation products are less toxic than the precursors (Escher et al., 2008a). However, there are also examples of pharmaceuticals whose degradation products, through exposure to light, are more toxic than the precursors (naproxen and diclofenac) (DellaGreca et al., 2004; Schulze et al., 2010), or are mutagenetic and genotoxic (ranitidine and gemfibrozil) (Isidori et al., 2007; Isidori et al., 2009). Some pharmaceuticals have first to be transformed in the body into an active metabolite to become effective – the antiviral oseltamivir, for example (Escher et al., 2010).

5.3 EFFECTS OF MIXTURES

The last few years have seen more and more research conducted into the effects of mixtures of pharmaceuticals. In many cases the mixture of two pharmaceuticals is involved, although sometimes the research studies mixtures of more pharmaceuticals from different groups (e.g., Henry & Black, 2007; Quinn et al., 2009; Backhaus et al., 2011; DeLorenzo & Fleming, 2008; Dietrich et al., 2010a; Dietrich et al., 2010b; Cleuvers, 2003).

The effects of mixing pharmaceuticals can often be predicted using concentration addition – which means that the effects of the individual pharmaceuticals can be added up – but interactions, such as the reinforcement of an effect, also occur regularly. If interactions do occur they are frequently not constant and depend, for instance, on the concentration and/or the period of exposure, but not in a consistent way. All of which renders modelling the effects difficult (Flaherty & Dodson, 2005).

A number of research projects tested the effects of mixtures of 11 to 13 pharmaceuticals, at concentration levels that are found in effluent (Quinn et al., 2009; Pomati et al.,2006; Pomati et al.,2007; Pomati et al.,2008). These mixtures had significant effects on the morphology and food consumption of hydra and on human and fish cell lines. Mixture effects were already observable at the ng/L level for the individual pharmaceuticals. These concentrations are only a few times higher than they are in the effluent. The mixture already had an effect at concentrations 100 to 1,000 times lower than did individual pharmaceuticals. This means that the mixture effects in environmental concentrations are real.

Not all mixtures have effects however. In the Netherlands, Alterra, on a commission from Water Board Regge and Dinkel, tested the toxicity of a mixture of 9 pharmaceuticals in a microcosm system (Roessink et al., 2012). The system contained water, sediment, water fleas, water lice, worms, snails and a water plant. The pharmaceuticals tested where those in the highest concentrations found in the effluent by Regge and Dinkel (Oosterhuis et al., 2011). An effluent was also subsequently tested. No negative effects on population density were observed either in the pharmaceutical mixture or in the effluent. The population densities were actually the highest in the effluent because of its high nutritional value. The absence of effects is in line with the predictions based on a risk assessment using PNEC values from the Swedish environmental classification system for pharmaceuticals (http://www.fass.se; calculations: Anja Derksen, AD eco advies).

5.4 TARGETED EFFECT MEASUREMENT IN EFFLUENTS AND SURFACE WATER

Effluents and receiving surface water contain a complex mixture of micropollutants, including pharmaceuticals. The effects of these micropollutants can be rendered visible using targeted effect measurements based on the mechanisms of action of the substances. Most studies into the effects of micropollutants in effluent and surface water make use of fish and mussels. Effluent feminizes fish and mussels, disturbs the immune system and neurochemistry, and biomarkers for the presence of substances and/or oxidative stress increase. Such effects are sometimes measurable up to 10 km downstream.

Hormone disrupting effects from natural and synthetic hormones[7] and nonylfenol (ethoxylates) are clear and have been frequently demonstrated (but are beyond the range of this report). With regard to the other effects, a number of studies suggest that pharmaceuticals are possibly responsible substances, that is, that pharmaceuticals in laboratory substance tests produced comparable effects to those observed in the effluent. These studies are briefly explained below.

A properly functioning immune system consists of a general line of defence and a specific line of defence. This specific defence comprises the complicated combined action of antibodies, different types of white blood cells and various transmitters. Fish and mussels show a number

7 Particularly the natural hormone oestrone, 17 beta oestradiol and the contraceptive pill's synthetic hormone (17alpha-ethinylestradiol). The two latter substances are candidate priority substances for the Water Framework Directive.

of measurable disturbances after being exposed to effluent, including a reduced immune response, an increase in the general defence and a decrease in the specific defence, or an increase in transmitters (Bouchard et al., 2009; Müller et al., 2009; Salo et al., 2007).
Research has also been conducted into the neurotoxicity for deployed and wild mussels upstream and downstream of and effluent. This investigation focused particularly on serotonin and dopamine, both neuro-transmitters, which are involved in a large number of processes, including cell signalling in the brain, behaviour, appetite, sexual maturation in fish and mussels, and the release of oocytes and spermatozoa (Gagné & Blaise, 2003). There are measurable effects in mussels in the effluent and the effluent plume in the receiving surface water on their dopamine and serotonin levels, and degradation enzymes and serotonin and dopamine transporter systems, for a downstream range of up to 10 km (Gagné & Blaise, 2003). The suggested responsible substances are oestrogens, nonylfenol and morphine (Gagné et al., 2010; Gagné et al., 2007a). Antidepressants and drugs could also be responsible because of their mechanisms of action.

In addition, measurements were also carried out on mussels for biomarkers ("biological indicators"). In mussels in effluent and effluent plumes, measurements showed a clear increase in the levels of enzymes involved in substance degradation, indicating the presence of micropollutants, such as oxidants, hormones, pharmaceuticals and other substances (Binelli et al., 2009; MartinDiaz et al., 2009; CartardaJara et al.,2009; CartardaJara et al. 2010; Franzellitti et al., 2011).

Additional treatment techniques at WWTPs could be an option to eliminate the effects observed in effluent (see paragraph 4.2). To test this, effect measurements were carried out in a number of WWTPs or pilot projects for additional treatment techniques (e.g., Kienle et al., 2011; Gagné et al., 2007b; Escher et al., 2008b; Escher et al., 2009). These effect measurements consisted of a bioassay test battery for general toxicity and/or specific toxicity (hormone disruption, dioxin-like effects, genotoxicity, phytotoxicity, neurotoxicity, early-life stage tests, etc.). Additional treatment steps seem to be capable of removing at least some of the effects. But there are indications that (toxic) degradation products are created during advanced oxidation processes (Abeggelen et al., 2010; Radjenovic et al., 2009; Reungoat et al., 2010). The toxicity appears to be a function of the ozone concentration used and of the treatment time, and the effects appear to be easy to remove, for instance, through sand filtration (Stalter et al., 2009; Stalter et al., 2010). Further research into the creation and removal of toxic degradation products is desirable.

The apparent effectiveness of an extra treatment step in improving the quality of the receiving stream is shown in a Swiss field study, in which amphipoda are deployed in the receiving water prior and after the application of a full-scale ozone treatment. Prior to the application, the food intake of the deployed amphipoda dropped (by up to 90% at 150 m from the discharge point); after the ozone treatment there was no decrease in food intake (Bundschuh et al., 2011).
In the Netherlands, in 2012, the WIPE research project was completed. This involved a large-scale study into the effects in WWTP effluent and in different steps of a water harmonica. A water harmonica is a wetland system located between the WWTP and the receiving stream, which is intended to improve the ecological quality of the water in particular, before it is discharged into the receiving stream. The project involved conducting biological and chemical measurements at three WWTPs at different locations in the treatment wetlands. These included chemical analyses and bioassays on extracts of the passive samplers and

research into the condition and reproductive success of sticklebacks in flow tanks (Foekema at al., 2012a). The chemical studies showed that pharmaceuticals constituted an average of 10% of all the substances found. The in vitro bioassays – e.g., for hormone disruption, cell toxicity and the effects of antibiotics – showed no great effects. But there was a lot of variation in the toxicity and its levels showed a decrease during the course through the treatment wetlands. The in vivo bioassays with bacteria, algae and water fleas suggested that chronic effects cannot be excluded. Nevertheless, the survival and reproduction of the sticklebacks in the flow tank were good. Genetic research in these fish also showed clear effects on the gene expression, which indicate the presence of feminizing and anti-feminizing substances, and the activation of degradation enzymes and the immune system. In comparison to other WWTPs, the effects found were lower than anticipated. It appears that the effluents studied were already relatively clean. The wetland system seems to have had a buffering effect and in this way equalised the toxicity peaks.

The effects of pharmaceuticals on the ecological quality of the receiving stream has not yet, or hardly, been closely researched. There is only one known study (Ginebreda et al., 2010), in which a correlation is found between concentrations of antibiotics and beta-blockers and the density and biomass of mosquito larvae and oliochaeta (worms). What has been shown is that fish swimming downstream show a behavioural change when confronted with a discharge plume of WWTP effluent. More than half of the fish changed their swimming path and tried to skirt around the edge of the discharge plume (Foekema at al., 2012b).

5.5 ASSESSMENTS OF PRESENCE IN SURFACE WATER

Official environmental quality standards for pharmaceuticals in surface water or other water matrices are (still) lacking. However, provisional environmental quality standards and/or provisional Predicted No Effect Concentrations do exist. These provisional environmental quality standards and PNEC values, and the derivation of these values, are discussed in Annex 6. The derived PNEC values and provisional environmental quality standards vary considerably, from 0.026 µg/L for the antibiotic ofloxacin to 320000 µg/L for the diuretic furosemide. For the contraceptive pill's synthetic female hormone, 17 alpha-ethinyloestradiol, the concentration is even extremely low, at 0.035 ng/L . This is (far) below the detection limit. This substance cannot therefore be measured with the sensitivity required to make a risk assessment. For diclofenac, which, like ethinyloestradiol, has been proposed for inclusion as a priority substance within the Water Framework Directive, the concentrations in surface water generally fall below the standard, while the maximum concentrations exceed the standard. Concentrations in effluent are on overage 2 to 3 times above the standard (Derksen, 2012). Van der Aa (2011c) found, based on a comparison of predicted environmental concentrations with derived provisional PNEC values, a risk regarding 2 of the 13 pharmaceuticals studied, namely, the antibiotic amoxicillin and the synthetic hormone ethinyloestradiol. It should be pointed out that the calculations of the environmental concentrations were made on the basis of consumption and excretion. No account is taken of the degradation during water treatment. Penicillins, like amoxicillin, are however effectively broken down during water treatment, so that the risk associated with this antibiotic is overestimated.

6

EFFECTS ON HUMANS

6.1 RISK ASSESSMENT OF EXPOSURE TO PHARMACEUTICALS IN DRINKING WATER

Humans can be exposed to very low concentrations of pharmaceuticals and their transformation products through drinking water. There are no legal quality standards regarding pharmaceuticals in drinking water or drinking water sources. There are, however, signalling values, target values and provisional limit values. Thus the new Dutch Decree on Water Quality (2011) has defined a signalling value of 1,0 μg/L for all anthropogenic substances. In addition, the "Q21" report, based on the so-called TTC (Threshold of Toxicological Concern) concept, contains a target value of 0.1 μg/L for all environmentally-alien substances that are not genotoxic or hormone disturbing (van der Kooij et al., 2010). The same target value is used in the Danube, Meuse and Rhine Memorandum (Wirtz et al., 2009). This standard is intentionally very conservative. This means that values below the target values are considered safe, but it does not immediately mean that an exceedence implies a risk (see Annex 7). Concentrations of pharmaceuticals in surface water frequently exceed the above-mentioned quality standards (Kümmerer, 2009; Monteiro and Boxall, 2010; Roig, 2010; RIWA, 2011a).

In order to assess more precisely whether exposure to these substances has an effect on health, a risk assessment can be conducted. For the conduct of such an assessment a provisional health limit value for drinking water needs to be derived. The details of this derivation are discussed in Annex 8. If the level of the concentration measured in drinking water is below this limit value, no effects on health are expected. If the level is above the limit, then additional research is recommended. Such limit values have been established for a few tens of pharmaceuticals. These limit values range between 1 μg/L for the beta-blocker bisoprolol and 415 mg/L for the iodinated X-ray contrast medium iopamidol (Versteeg et al., 2003 & 2007; Schriks et al., 2010; van der Aa et al., 2011a; De Jongh et al., 2012). Current research indicates that there is a wide margin between the derived provisional health limit values and the concentrations measured and found in drinking water and drinking water sources.

6.2 PROCEDURE TO DETERMINE THE EFFECTS OF MIXTURES

A health limit value for drinking water is based on the toxicity data for a single substance. A limitation of these substance-specific risk assessments is that they do not take account of long-term, simultaneous exposure to several substances. In order to say something of the effects of mixtures, two research projects took into consideration the accumulation of the toxicological effects of substances, by setting health limit values for groups of pharmaceuticals with the same mode of action (van der Aa et al., 2011a; De Jongh et al., 2012). This approach compares the concentration addition of the pharmaceuticals and transformation products within a specific group to the limit values set for the group. This group limit value is established at a level equal to the lowest substance-specific limit value within the group. The approach is based on the principle of dose additivity, whereby theoretically the total effect of a substance is equal to the result of the multiplication of its concentration by its toxic potency, and the

mixture's total effect is equal to the addition of the effects of all its components (Jonker et al., 2004). For example, if three beta-blockers and one degradation product of one of the beta-blockers are found at a concentration of 0.1 µg/L, these concentrations are added up and jointly tested as a single, combined value.

Even when dose additivity is applied, and when concentrations of the targeted pharmaceuticals and transformation products are grouped by mode of actions, the levels in drinking water remain significantly below the derived health limit values (van der Aa et al., 2011a; De Jongh et al., 2012).

Possible synergy interactions in the mixtures, whereby the combined effect is greater than the sum of that of the constituent parts, have however not be considered. A recent publication does nevertheless show that dose additivity does play a role primarily in cases of low concentrations and that synergy effects are less probable (Boobis et al., 2011). But a clearer understanding of interactions between substances in mixtures is still important for the development and improvement of future health limit values.

7

POSSIBLE TECHNICAL MEASURES

7.1 COSTS OF MEASURES FOR (SUPPLEMENTARY) WWTP TREATMENT

The Policy Letter to the Lower House (Tweede Kamer, 2007) proposed a number of source measures, some of which have since been implemented (Tweede Kamer, 2009). These include measures related to Green Pharmacy (to stimulate the development of more easily degradable pharmaceuticals), information about the return of unused pharmaceuticals and effective use of pharmaceuticals. Technical measures were also put forth, namely, to reduce emissions by applying treatment techniques at the sources of the pharmaceuticals before they reach the wastewater (prior to the connection with the sewerage system), as well as end-of-pipe treatment measures (at WWTPs). The possibilities of these source and end-of-pipe measures are being explored.

Pharmaceuticals can be removed from various waste streams: urine, faeces, a combined stream of urine and faeces, the wastewater of healthcare institutions, or at WWTPs. Here are a few of the (ongoing) projects in which the various waste streams are dealt with separately:

1 SLIK – development of a treatment concept for the hospital's entire wastewater stream,; in collaboration with the Isala Klinieken in Zwolle, the Groot Salland Water Board, Vitens, the Province of Overijssel, the municipality of Zwolle, STOWA and RIVM. See http://www.wgs.nl/schoon water/slik(pills)/.
2 Sleen – separate collection of, and removal of pharmaceuticals from, urine at a nursing home; collaboration including STOWA and the Velt and Vecht Water Board. See http://www.veltenvecht.nl/projecten/ anders_plassen.
3 Pharma filter at the Reinier de Graaf Gasthuis hospital in Delft – this is an integrated concept for the processing of waste streams of hospitals and healthcare institutions; collaboration including Delfland Water Board and STOWA. See www.pharmafilter.nl.
4 SOURCE in Boxmeer – research project on the treatment of human and animal urine for the recovery of phosphorus, removal of nitrogen and removal of pharmaceuticals; collaboration including the Aa en Maas Water Board, the Province of North-Brabant, ZLTO, STOWA and Ministry of Economic Affairs, Agriculture and Innovation (Mulder et al., 2011).

It can generally be noted that the costs of additional treatment techniques depend essentially on the treated volume . This means that the treatment of concentrated wastewater streams can be a good option from a cost perspective. In biological wastewater treatment, the aeration is the key cost component. These costs are however a function of the waste load rather than the volume.

Annex 9 presents the preferred techniques for the removal of pharmaceuticals at WWTPs, as defined in Grontmij (2011a). The implementation of additional treatment techniques at all WWTPs would involve an additional annual expense of about € 800 million, assuming an optimal implementation of ozone and activated carbon (77% removal of the total pharmaceutical load in the WWTP's effluent). A less extensive removal, using only activated

carbon filtration and resulting in a 60% removal, would cost about € 570 million (Grontmij, 2011a).

It is also possible to prioritise the WWTPs to be targeted. This can be done on the basis of reducing the loads of human pharmaceuticals discharged into the surface water (load approach), or on the basis of the concentration of human pharmaceuticals in the receiving water (concentration approach). In Switzerland the choice was made for a combination of the two approaches. In other words, the WWTPs targeted: 1) have a treatment capacity >100,000 i.e., 2) have effluent that constitutes a significant proportion (>10%) of the receiving surface water, and 3) discharge into bodies of water of which the surface water is used for the production of drinking water.[8]

The choice made has a strong impact on annual costs. Grontmij (2011a) estimates that the annual costs of targeting only large WWTPs (> 100,000 i.e.) that discharge into small, vulnerable surface water would amount to about € 90 million.

To put these costs in perspective: in 2011, the net cost of wastewater treatment was € 46 per inhabitant equivalent (i.e.), and 22.5 million i.e. were processed in the Netherlands (cited by Michael Bentvelsen, UvW). The annual net treatment costs therefore amounted to € 1,035 million. The aforementioned treatment options therefore represent a cost increase in net treatment costs of 8.7% to 77%.

7.2 COST OF MEASURES FOR (SUPPLEMENTARY) DRINKING WATER TREATMENT

In the Netherlands, 58% of drinking water is produced from groundwater, 37% from surface water and 6% from bank-filtered water (Geudens, 2012). The water is purified using a variety of techniques. After being used, human pharmaceuticals tend to end up mainly in surface water. It thus makes sense to look first at the drinking water production locations that use surface water or bank-filtered water for their sources. A determination can be made for these locations of the extent to which the source contains pharmaceuticals and other micropollutants and the degree to which current treatment removes them.

A robust drinking water purification process is made up of several sequential barriers using different techniques. Which specific combination of techniques is the most effective depends on the composition of the water to be purified – salinity, pH, type and content of natural organic material, presence of nitrate and bicarbonate, etc. The entire treatment process, including any supplementary advanced purification techniques (see paragraph 4.3) will determine the extent of the removal of pharmaceuticals (and other micropollutants). Lastly, a determination can be made of what extra costs these supplementary techniques involve. These costs include investment costs as well as a variety of operational costs: energy, maintenance, materials and residual-stream processing.

Each technology has its own advantages and disadvantages. Activated carbon filtration, for example, requires little energy, but the carbon has to be regularly regenerated thermally, which results in a loss of about 10% of the material. The frequency of this regeneration depends on the composition of the water. Purification of bank-filtration water, with a high organic material content, requires carbon regeneration once or twice a year, while the biological activated carbon filtration used in the purification of drinking water in Amsterdam

8 http://www.bafu.admin.ch/dokumentation/medieninformation/00962/index.html?lang=de&msgid=35168

only requires a regeneration once every two years. Activated carbon filtration typically costs between € 0.10 and € 0.20 per m^2 of purified water. Other adsorbents can also be employed (Bauerlein et al., 2012a). But these "new" adsorbents are not available on a large scale and their regeneration possibilities and costs are unknown to date. Membrane processes generally cost more than activated carbon filtration, and one has also to take account of the concentrate stream they produce, which sometimes requires further treatment and ultimately must also be discharged. Advanced oxidation processes are also more costly than activated carbon filtration. These techniques can also result in the formation of by-products, which might be harmful and have to be removed through supplementary activated carbon filtration (Heringa et al., 2011).

As yet, no extensive national inventory has been drawn up of the locations where additional treatment techniques would make sense if there were a desire to remove pharmaceuticals (and other micropollutants) from drinking water. Nor is there an understanding of which treatment techniques – or combination of techniques – would produce the best results at each location, or what the associated investment and operational costs would be. For this reason, it is not yet possible to estimate the costs of any measures taken to exclude pharmaceuticals from drinking water. The lack of this information means that there is a need for an inventory of the costs and benefits of the implementation of additional treatment techniques at drinking water production locations in the Netherlands.

8

SYNTHESIS

8.1 SUMMARY

Targeted research and broad screening, both in the Netherlands and internationally, has found widespread presence of pharmaceuticals in the water cycle. More recently, the degradation products of pharmaceuticals – which are formed in humans, water treatment and the environment – have also been the object of research. It appears that these substances can occur in the water cycle in concentrations comparable to those of their precursors.

By far the most important route of pharmaceuticals into surface water is via WWTPs: after being used, the pharmaceuticals are excreted and are transported to the WWTP through the sewerage system. The largest proportion of pharmaceuticals in WWTP influent originates in residential areas. Generally speaking, less than 10% comes from hospitals, 1-5% from other healthcare institutions, while the contribution of industry is minimal. At the local level, however, the different contributions of these sources can vary significantly.

WWTPs remove a large proportion of the pharmaceuticals (65% on average). The remainder is thus discharged with the effluent into the surface water. Pharmaceuticals are found in effluent at levels ranging up to more than 100 µg/L; for the most part they consist of the antidiabetic metformin and its degradation product guanylurea, X-ray contrast media, beta-blockers, painkillers, antiepileptics and antibiotics. Typically, concentrations in large rivers amount to a few µg/L, while concentrations in smaller bodies of surface water that are heavily loaded with WWTP effluent have been measured at tens of µg/L. Groundwater usually contains no pharmaceuticals. In bank-filtration water a number of very mobile and persistent pharmaceuticals and degradation products have been found at concentrations of tens and sometimes hundreds of ng/L. Traces of pharmaceuticals (ng/L level) are sometimes found in drinking water. The concentrations and loads encountered in the large rivers are, for specific pharmaceuticals, at least as high as those of “classical” substances, such as the priority substances of the European Water Framework Directive.

At this moment, there is no official (legal) test framework to assess the presence of pharmaceuticals in the water cycle. Signalling values and target values have, however, been formulated, and provisional Predicted No Effect Concentrations have been derived. The necessity and utility of emission reduction measures is a subject of much discussion. Two concerns are at stake: having surface water of good quality, that is, the ecological concern, and having clean sources for the production of drinking water, which is a public health concern.

Little is known however about the presence and the risks of degradation products. Any observed effects could provide strong motivation for the implementation of emission reduction measures. There is currently no consistent strategy for the monitoring of the effects of pharmaceuticals (and other micropollutants) in wastewater, surface water and

drinking water. In view of the nature of the exposure and of the substances concerned, the assessment of the effects should focus on chronic exposure, on effects based on the mode of action (specific effects), and on the effects of complex mixtures of substances. This calls for another type of monitoring. The biological measurement methods for effects of these types are in part still under development. The results vary, and the inevitable uncertainties and ambiguities are pertinent too. Nevertheless, on the basis of the current state of knowledge, the effects in wastewater and surface water at environmental concentrations are real, if the chronic, specific and mixture effects are included in the risk assessment of pharmaceuticals. The risk to humans of the concentrations found of individual pharmaceuticals in drinking water is considered minor. But their presence in drinking water is undesirable because the effects of complex mixtures is difficult to estimate. The precautionary principle applies in this instance.

The WWTP is a logical focus for emission reduction measures. Such measures would result in improved water quality, which has ecological benefits and also lessens the intensity of treatment in drinking water production. Extending the treatment process to include, for instance, oxidation and adsorption steps could result in a maximum increase in annual net wastewater treatment costs from about € 1 billion to about € 1.8 billion, which represents a 77% increase if all WWTPs are adapted. If other options were chosen, such as only adapting some of the WWTPs or implementing less extensive additional treatment processes, the costs would be lower. A great advantage of targeting measures at WWTPs is that, apart from pharmaceuticals, emissions would be reduced for a wide range of other micropollutants stemming from personal care products or household products, such as softening agents, flame retardants, preservatives, fragrances, biocides and UV filters. The Dutch WWTPs are however not the only source of micropollutants in the water cycle. Micropollutants also reach surface water from the atmosphere, and through leaching and runoff. Moreover, a significant proportion of surface water micropollutants flow into the Netherlands from other countries. Possible emission reduction measures should therefore be taken internationally, per river basin. It would also be desirable to simultaneously tackle pharmaceuticals at source, for example, by developing more easily degradable pharmaceuticals (Green Pharmacy), prescribing fewer pharmaceuticals, or, when there is a choice, opting for the pharmaceutical with the lowest environmental impact.

8.2 KNOWLEDGE GAPS

The sources and emission routes of pharmaceuticals are well known. Fluctuations in emissions, treatment efficiency and hydrological circumstances can however result in large differences in concentrations both in terms of space and time. The pharmaceutical loads in river basins are frequently the object of modelling abroad. Such area studies are for the most part still largely lacking for the Dutch water system.

In addition, more attention should be paid to the formation, persistence and effects of degradation products, which are formed in humans, WWTPs, surface water and drinking water production. Little is actually known about this category of substances, while their environmental concentrations are comparable to those of their precursors, and they can be persistent and toxic.

The toxicological assessment of substances is usually undertaken at the level of the individual substance. But pharmaceuticals, degradation products (and other wastewater-related

substances) are present in complex mixtures, the long-term effects of which, particularly on the ecosystem, are not sufficiently known.

The removal efficiency for pharmaceuticals (and other wastewater-related substances) of the different treatment techniques have been charted in part. On this basis, generic removal percentage figures have been derived for different techniques. There are, however, large differences between the substances and treatments, furthermore treatment efficiencies can vary in time. The key elements – i.e., substance properties, treatment design and operational management, seasonal influences and/or hydraulic conditions – are as yet not sufficiently understood. It would be desirable, on the basis of recent Dutch and international research, to conduct a solidly-founded appraisal of the technical and financial aspects involved. Account would also have to be taken of energy consumption, CO_2 emissions, reuse of raw materials, such as nitrogen and phosphorus, and any waste streams created. This appraisal should be location- and situation-specific. One would expect that such an appraisal process could be completed in a few years.

8.3 POINTS OF PARTICULAR INTEREST

This state-of-the-science report shows that a lot is known about the presence and behaviour of human pharmaceuticals in the water cycle. Knowledge about the risks is more limited. This report can provide the foundation for the design of research and policy over the short and long term. To this end, a number of points of particular interest have been formulated:

NO TEST FRAMEWORK

At this point in time, the legal frameworks do not contain any (environmental) quality standards for pharmaceuticals in the water cycle. Generic signalling values and target values are however regularly exceeded. The lack of a legal test framework can be seen as an obstacle to the implementation of measures, because without such a test framework it is hard to adequately answer the question: How serious is the presence of these concentrations of pharmaceuticals in the water?, and therefore to provide a basis for the development of measures. This calls for the derivation of quality standards and for their incorporation into legal frameworks, or for the use of alternatives such as target values, Predicted No Effect Concentrations (PNECs) or biological effect measurements.

NON-TECHNICAL MEASURES

Non-technical emission reduction measures, such as those contained in the Policy Letter (Tweede Kamer, 2007), are beyond the range of this report. This does not mean however that these measures are not important in the effort to reduce pharmaceutical emissions.

DRINKING WATER OF IMPECCABLE QUALITY

Although provisional toxicological evaluations have turned out to be “reassuring” and concentrations are far below risk levels, drinking water companies abide by the precautionary principle: they provide water of impeccable quality. The presence of pharmaceuticals and other substances in water sources and in produced drinking water is not compatible with this principle. The uncertainties mentioned with regard to degradation products, mixture toxicity and article 7 of the WFD are also pertinent.

CONNECTION WITH OTHER MICROPOLLUTANTS

Measures for emission reduction for pharmaceuticals have also to take micropollutants into

consideration. WWTP effluent contains loads of "other" micropollutants, such as softening agents, flame retardants, preservatives, fragrances, biocides and UV filters, that are many times larger (> 10 times) than those of human pharmaceuticals (Grontmij, 2011a). Better removal of pharmaceuticals in the WWTP also results in an emission reduction of "other" wastewater-related micropollutants. However, such measures do not, or hardly, reduce emissions of micropollutants like plant protection products, certain industrial substances and veterinary pharmaceuticals, since the emission routes of these substance groups do not primarily involve wastewater streams.

NATIONAL AND INTERNATIONAL COLLABORATION

More than half of the pharmaceutical loads in the Rhine and Meuse originates outside of the Netherlands. An improvement of the quality of the country's surface water therefore requires that this load from abroad be reduced. In Switzerland,[9] upstream on the Rhine, concrete measures have already been taken and a national policy is being developed. In addition, in Germany, at different locations and upon local initiative, WWTPs are being extended to include extra treatment steps.[10] This should in the future probably reduce the load transported into the Netherlands by the Rhine. In the Meuse basin (Belgium) the effort is being concentrated primarily on connecting a larger proportion of households to the WWTPs and on improving treatment and capacity (SPGE, 2006). The fact that a significant portion of the pharmaceutical load in the large rivers originates abroad calls for international collaboration in the river basins for the joint reduction of the emissions.

PRIORITISING (WHICH SUBSTANCES DESERVE MORE ATTENTION)

The analysis lists of pharmaceuticals have grown with time, so that, to begin with, a number of substances or substance groups were selected for analysis on the basis of the expectation that they could be found and of the existence of analysis methods for them. For many years, research concentrated on these substances and substance groups. Slowly, however, the realisation grew that these were possibly not the substances that always presented the greatest risks, in terms of concentrations, loads and/or (eco)toxicity.

Attempts have been made within a variety of contexts to prioritise pharmaceuticals, usually on the basis of an estimate of exposure and toxicity (Mons et al., 2003; Derksen et al., 2007; de Voogt et al., 2009; van der Aa et al., 2011b; van der Aa et al., 2011c; STOWA, 2011c; AquaSense, 2003; Roos et al., 2012; NORMAN, 2009; Besse & Garric, 2007). These prioritisations provide guidance for measurement programmes and effect studies. They moreover contribute to a better understanding of the risks of pharmaceuticals for humans and the environment.

It is striking that substances that act on the nervous system and cardiovascular agents usually score high in the various environmental prioritisations (STOWA, 2007a; STOWA 2011c; AquaSense, 2003; Roos et al., 2012, Besse & Garric, 2007). Measurements taken in 2011 within the framework of FATE-SEES (a European-wide WWTP effluent monitoring campaign)

9 The planning for measures in Switzerland is at an advanced stage of elaboration. The parliament has decided to implement extensive treatment techniques in:
WWTPs with treatment capacities of >100,000 ie;
WWTPs whose effluent constitutes a significant proportion (>10%) of the receiving surface water;
WWTPs that discharge into bodies of water of which the surface water is used for the production of drinking water.
The WWTPs have to be adapted within a period of 15 years. Two techniques have been proposed: 1) Pulverised coal followed by sand filtration and 2) Ozone plus a biological sand filter. The estimated costs for a WWTP of 100,000 i.e. are, respectively, € 21.00 and € 9.10 per i.e. The proposed financing of these measures, on the basis of "polluter pays" principle, is open for perusal until August 2012. For up-to-date information, visit www.bafu.admin.ch.r

10 See http://www.masterplanwasser.nrw.de.

included a number of pharmaceuticals that had never before been measured. Nervous system and cardiovascular agents were encountered in surprisingly high concentrations. These substances therefore certainly deserve extra attention.

ONLY A LIMITED NUMBER OF SUBSTANCES CAN BE RESEARCHED

Only about a quarter of the pharmaceuticals in use are currently the object of studies for their presence in the environment and/or drinking water. Because of the lack of analysis methods it is not yet possible to make measurements of all pharmaceuticals in the water cycle. This, in itself, is not necessary, since the presence of a specific set of pharmaceuticals can be used as an indicator of the presence of other pharmaceuticals and degradation products. Several pharmaceuticals have been proposed as tracers for the wastewater loads in groundwater and surface water. These include: carbamazepine, iopamidol, amidotrizoine acid, sulfamethoxazole, phenazone, propyphenazone, primidone and crotamiton (Fenz et al., 2005a; Fenz et al., 2005b; Clara et al., 2004; Kahle et al., 2009; Kuroda et al., 2012; Scheurer et al., 2011; Sadezky et al., 2008; Nakada et al., 2008). Sweeteners, such as acesulfameK, can also be used as tracers for wastewater loads (including pharmaceuticals) (Lange et al., 2012). Clofibrin acid can be used as a tracer for historical wastewater loads (Sadezky et al., 2008).

8.4 RECOMMENDATIONS

- Monitoring data on pharmaceuticals is very scattered. Connecting databases unlock the data and make them more accessible. All Dutch monitoring data can also be entered into EMPODAT, the database of the European NORMAN network.[11] Entering data in EMPODAT makes it possible to compare these data to those of other European countries. The monitoring data can then be used in the European prioritisation of emerging substances.
- A test framework would increase the possibility of indicating the presence and risks associated with pharmaceuticals in the water cycle. Over the long run, this calls for the derivation of (environmental) quality standards. In the short run, alternatives to quality standards can be applied, for example, target values, Predicted No Effect Concentrations (PNECs), biological effect measurements and precautionary values like the Threshold of Toxicological Concern. Use could be made of the PNEC values derived in the Swedish Environmental Classification and Information System (SECIS) for pharmaceuticals (www.fass.se), or of those to be derived in the years to come in the NORMAN network as a result of the work of its Prioritisation of Emerging Substances Working Group (www.norman-netwerk.net). Another alternative would be to derive effect-directed quality standards on the basis of biological effect measurements.
- The effects in wastewater and drinking water could be measured using an integrated measurement strategy, whereby chemical and biological effect measurements are combined. There are a number of reasons to incorporate biological effect measurements, including:

a only a limited number of chemical substances are, and can be, measured,
b what matters ultimately are the effects of all contaminants together (from the risk perspective, which specific substances are responsible for the effect is less relevant),
c the demonstration of effects is an important stimulus for the taking of measures,
d the conduct of specific bioassays (i.e., bioassays that measure a specific mode of action, and provide insight into the nature of the risks, the substance groups responsible and therefore the possible sources, and into the measures that could be taken).

11 The EMPODAT database contains monitoring data on “emerging substances” in European environmental samples. Discussions are currently ongoing concerning whether drinking water data should be entered in this database.

It is therefore desirable that future measurement programmes focus on measuring effects that also provide insight into the presence and effects of specific groups of emerging substances. In addition, sampling methods could also be used – for both chemical and biological determinations – that provide insight into concentrations over longer periods of time (passive sampling).

- Knowledge about removal efficiency of pharmaceuticals (and other micropollutants) of the different treatment techniques and the key elements (substance properties, treatment design and operational management, seasonal influences and/or hydraulic conditions) need to be better understood. It is recommended that, on the basis of recent Dutch and international research, the technical aspects and cost-effectiveness be further elaborated and a comprehensive picture outlined. This should also cover other aspects such as energy consumption, CO_2 emissions, reuse of raw materials, such as nitrogen and phosphorus, and the creation of waste streams.
- The outlined overall picture can contain significant local variations. Area studies, which incorporate knowledge of the local situation, provide a detailed local picture and make it possible to prioritise locations and measures in an area-targeted manner.
- International collaboration on reducing emissions of pharmaceuticals (and other micropollutants) at the river-basin level need to be further strengthened and extended.

LITERATURE

Abegglen, C., B. Escher, A. Häner, C. Ort & M. Schärer (2010). Ozonung von gereinigtem Abwasser zur Elimination von organischen Spurenstoffen. Großtechnischer Pilotversuch Regensdorf (Schweiz). KA Korrespondenz Abwasser, Abfall 57(2): 155-160.

Ågerstrand M, Rudén C. 2010. Evaluation of the accuracy and consistency of the Swedish Environmental Classification and Information System for pharmaceuticals. Sci Total Environ 408: 2327-2339.

Ankley, G.T., M.C. Black, J. Garric, T.H. Hutchinson and T. Iguchi (2005). A framework for assessing the hazard of pharmaceutical materials to aquatic species. In: R.T. Willieam (Ed.). Science for assessing the impacts of human pharmaceutical materials on aquatic ecosystems, SETAC Press, Pensacola, FL. pp. 183-238.

AquaSense (2003). Ecotoxicologie van (dier)geneesmiddelen Plan van aanpak. In opdracht van: Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling (RIZA). AquaSense, Amsterdam. Rapportnummer: 1690-4.

Backhaus, T., T. Porsbring, A. Arrhenius, S. Brosche, P. Johansson & H. Blanck (2011). Single-substance and mixture toxicity of five pharmaceuticals and personal care products to marine periphyton communities. Environ Toxicol Chem. 30(9): 2030-2040.

Bauerlein, P.S., Mansell, J.E., ter laak, T.L., de Voogt, P., 2012. Sorption behavior of charged and non-charged polar organic compounds on SPE materials – Which functional group governs sorption? Environmental Science & Technology, 954-961.

Bauerlein, P.S., ter Laak, T.L., Hofman-Caris, R.C.H.M., de Voogt, P., Droge, S.T.J., 2011. Removal of charged micropollutants from water by ion-exchange polymers – effects of competing electrolytes. in press.

Berninger JP, Du B, Connors KA, Eytcheson SA, Kolkmeier MA, Prosser KN, Valenti TW Jr, Chambliss CK, Brooks BW. (2011). Effects of the antihistamine diphenhydramine on selected aquatic organisms. Environ Toxicol Chem. 30(9): 2065-2072.

Besse J.P. & J. Garric (2007). Médicaments à usage humain: risque d'exposition et effets sur les milieux récepteurs. Proposition d'une liste de médicaments à usage humain à surveiller dans les eaux de surface continentales. Cemagraf, Agence de l'Eau R.M.C., Lyon, 241 p.

Binelli A, Parolini M, Cogni D, Pedriali A, Provini A. (2009). A multi-biomarker assessment of the impact of the antibacterial trimethoprim on the non-target organism Zebra mussel (Dreissena polymorpha). Comp Biochem Physiol C Toxicol Pharmacol. 150(3): 329-336.

Blom, A.Th.G., J.C.M.J. de Bruijn & J.G.A.M. de Jong (1995). Verspilling. Faculteit Farmacie, Universiteit Utrecht, Utrecht.

Boobis, A., Budinsky, R., Collie, S., Crofton, K., Embry, M., Felter, S., Hertzberg, R., Kopp, D., Mihlan, G., Mumtaz, M., Price, P., Solomon, K., Teuschler, L., Yang, R., Zaleski, R., 2011. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment. Critical Reviews in Toxicology 41, 369-383.

Boxall A., Backaus T., Brooks B., Gouy D., Hickman S., Kidd K., Metcalfe C., Netherton M., Parrott J., Smith E., Straub J.O. and Weeks J. (2008). Report on environmental impact and health effects of PPs, KNAPPE (Knowledge and Need Assessment on Pharmaceutical Products in Environmental waters). European Project FP6, contract nr 036864. Deliverable number: D4.2.

Bouchard B, Gagné F, Fortier M, Fournier M. (2009). An in-situ study of the impacts of urban wastewater on the immune and reproductive systems of the freshwater mussel Elliptio complanata. Comp Biochem Physiol C Toxicol Pharmacol. 150(2): 132-140.

Bundschuh M, Pierstorf R, Schreiber WH, Schulz R. (2011). Positive Effects of Wastewater Ozonation Displayed by in Situ Bioassays in the Receiving Stream. Environ Sci Technol. 45(8): 3774–3780.

Clara M., Strenn B., & Kreuzinger N. (2004). Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behaviour of Carbamazepine in wastewater treatment and during groundwater infiltration. Water Res. 38(4):947-954.

Clara, M., B. Strenn, O. Gans, E. Martinez, N. Kreuzinger and H. Kroiss (2005). Removal of selected pharmaceuticals, fragrances and endocrine disrupting compounds in a membrane bioreactor and conventional wastewater treatment plants. Water Research 39(19): 4797-4807.

Cleuvers, M. (2003). Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects - Short communication. Toxicology Letters 142(3): 185-194.

Contardo-Jara V., Krueger A., Exner H.J., Wiegand C.(2009). Biotransformation and antioxidant enzymes of Dreissena polymorpha for detection of site impact in watercourses of Berlin. J Environ Monit. 11(6): 1147-1156.

Contardo-Jara, V., S. Pflugmacher, G. Nützmann, W. Kloas and C. Wiegand (2010). The β-receptor blocker metoprolol alters detoxification processes in the non-target organism Dreissena polymorpha. Environmental Pollution 158(6): 2059-2066.

Cunningham, V.L., M. Buzby, T. Hutchinson, F. Mastrocco, N. Parke and N. Roden, 2006. Effects of human pharmaceuticals on aquatic life: next steps. How do human pharmaceuticals get into the environment, and what are their effects? Environmental Science & Technology 40(11): 3456-3462.

de Graaff, M., Hofman-Caris, R., Bäuerlein, P., 2011. Affinity adsorption for the removal of micropollutants from (waste)water – a feasibility study. KWR Watercycle Research Institute, Nieuwegein, The Netherlands.

de Jongh, C.M., Kooij, P.J., De Voogt, P., Ter Laak, T.L., 2012. Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water. Science of the Total Environment 427-428, 70-77.

de Voogt, P., Janex-Habibi, M.-L., Sacher, F., Puijker, L.M., Mons, M., 2009. Development of a common priority list of pharmaceuticals relevant for the water cycle. Water Sci Technol 59, 39-46.

DellaGreca, M., M. Brigante, M. Isidori, A. Nardelli, L. Previtera, M. Rubino & F. Temussi (2004). Phototransformation and ecotoxicity of the drug Naproxen-Na. Environmental Chemistry Letters 1(4): 237-241,

Derksen, J.G.M. & J.H. Roorda (2005). Ketenanalyse humane en veterinaire geneesmiddelen in het watermilieu. In opdracht van het Ministerie van Volksgezond, Ruimtelijke Ordening en milieu (VROM). Grontmij, Amsterdam/De Bilt/Houten. Grontmij rapportnummer 9908421.

Derksen, J.G.M. (2012). Overview of European monitoring results of E2, EE2 and diclofenac in relation to the new EQS. Prepared by Anja Derksen, AD eco advice, Amsterdam, the Netherlands, Februari 7th, 2012 commissioned by the Dutch Association of Regional Water Authorities.

Dietrich, S., S Dammel, F. Ploessl, F. Bracher & C. Laforsch (2010a). Effects of a pharmaceutical mixture at environmentally relevant concentrations on the amphipod Gammarus fossarum. Marine and Freshwater Research 61(2) 196–203.

Dietrich, S., F. Ploessl, F. Bracher & C. Laforsch (2010b). Single and combined toxicity of pharmaceuticals at environmentally relevant concentrations in Daphnia magna – A multigenerational study. Chemosphere 79(1): 60-66.

DeLorenzo, M.E. & J. Fleming J. (2008). Individual and mixture effects of selected pharmaceuticals and personal care products on the marine phytoplankton species Dunaliella tertiolecta. Arch Environ Contam Toxicol. 54(2):203-210.

EC (2001). Directive 2001/83/EC of the European Parliament an of the council of 6 November 2001 on the Community code relating to medicinal products for human use.

EC (2004). Directive 2004/27/EC EC of the European Parliament an of the council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (text with EEA relevance).

Elzen, den J.J.M. & A. Malsch (2009). Broninventarisatie Rijnlandse probleemstoffen. Emissie vanuit de AWZI's. Hoogheemraadschap van Rijnland, Leiden.

EMEA (2006a). Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00. European Medicines Evaluation Agency, London.

EMEA (2006b). Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00 corr 1. European Medicines Evaluation Agency, London.

ECHA. 2008. Guidance on information requirements and chemical safety assessment. Chapter R.10: Characteristics of dose [concentration]-response for environment. Helsinki, Finland: European Chemicals Agency. Report no. R.10. 65 pp.

Escher, B.I., N. Bramaz, R.I. Eggen, M. Richter (2005). In vitro assessment of modes of toxic action of pharmaceuticals in aquatic life. Environ Sci Technol. 39(9): 3090-3100.

Escher, B.I., N. Bramaz, M. Richter & J. Lienert (2006). Comparative ecotoxicological hazard assessment of beta-blockers and their human metabolites using a mode-of-action-based test battery and a QSAR approach. Environ Sci Technol. 40(23): 7402-7408.

Escher, B., Baumgartner, R., Lienert, J., Fenner, K., (2008a). Predicting the ecotoxicological effects of transformation products. Hdb Env Chem 2.

Escher B.I., Bramaz N., Quayle P., Rutishauser S., Vermeirssen E.L. (2008b). Monitoring of the ecotoxicological hazard potential by polar organic micropollutants in sewage treatment plants and surface waters using a mode-of-action based test battery. J Environ Monit. 10(5): 622-631.

Escher B.I., Bramaz N., Ort C. (2009). Monitoring the treatment efficiency of a full scale ozonation on a sewage treatment plant with a mode-of-action based test battery. J Environ Monit. 11(10): 1836-1846.

Escher, B.I., N. Bramaz, J. Lienert, J. Neuwoehner & J.O. Straub (2010). Mixture toxicity of the antiviral drug Tamiflu((R)) (oseltamivir ethylester) and its active metabolite oseltamivir acid. Aquat Toxicol. 96(3): 194-202.

Escher, B.I., Fenner, K., 2011. Recent Advances in Environmental Risk Assessment of Transformation Products. Environmental Science & Technology 45, 3835-3847.

European Commission (2012). Proposal for a directive of the European Parliament and of the Council, amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. COM(2011) 876 final.

Fent, K., Weston, A.A., Caminada, D., 2006. Ecotoxicology of human pharmaceuticals. Aquatic Toxicology 76, 122-159.

Fent, K., A.A. Weston & D. Caminada (2006). Ecotoxicology of human pharmaceuticals. Aquatic Toxicology 76(2): 122-159. Erratum in Aquatic Toxicology 78(2): 207.

Fenz R, Blaschke AP, Clara M, Kroiss H, Mascher D, Zessner M. (2005). Monitoring of carbamazepine concentrations in wastewater and groundwater to quantify sewer leakage. Water Sci Technol. 2005;52(5):205-13.

Fenz R, Blaschke AP, Clara M, Kroiss H, Mascher D, Zessner M. (2005). Quantification of sewer exfiltration using the anti-epileptic drug carbamazepine as marker species for wastewater. Water Sci Technol. 2005;52(9):209-17.

Flaherty, C.M. & S.I. Dodson (2005). Effects of pharmaceuticals on Daphnia survival, growth, and reproduction. Chemosphere 61(2): 200-207.

Foekema et al. (2012a). De invloed van moerrassystemen op de milieukwaliteit van rwzi effluent en aanbevelingen tot optimalisering. IMARES rapport C005/12.

Foekema, E.M., H.V. Winter, F. Kleissen, O.A. van Keeken, A.D. Rippen & D.M.E. Slijkerman (2012b). Vismigratie en lozingspluimen: Samenvattend rapport. IMARES Wageningen UR, Den Helder. Rapport C077/11. In opdracht van Innovatieprogramma Kaderrichtlijn Water van het ministerie van Infrastructuur en Milieu.

Fong, P.P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. Biol. Bull. 194: 143-149.

Fong. P.P., P.T. Hulminski & L.M. D'Urso (1998). Induction and potentation of parturition in fingernail clams (Sphaerium striatinum) by Selective Serotonin Re-Uptake Inhibitors (SSRIs). The Journal of Experimental Zoology 280: 260-264.

Fong, P.P. (2001). Antidepressants in aquatic organisms: a wide range of effects. In: C.G. Daughton & T.L. Jones-Lepp (eds.). Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, Symposium Series 791; American Chemical Society: Washington, D.C.. ACS/ Oxford University Press. p264-281.

Franzellitti S, Buratti S, Valbonesi P, Capuzzo A, Fabbri E. (2011). The βblocker propranolol affects cAMP-dependent signaling and induces the stress response in Mediterranean mussels, Mytilus galloprovincialis. Aquat Toxicol. 101(2): 299-308.

Fritzmann, C., Löwenberg, J., Wintgens, T., Melin, T., 2007. State-of-the-art of reverse osmosis desalination. Desalination 216, 1-76.

Gagné, F. and C. Blaise (2003). Effects of municipal effluents on serotonin and dopamine levels in the freshwater mussel Elliptio complanata. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 136(2): 117-125.

Gagné, F., C. Blaise, M. Fournier and P.D. Hansen (2006). Effects of selected pharmaceutical products on phagocytic activity in Elliptio complanata mussels. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 143(2): 179-186.

Gagné F., Blaise C., André C., Gagnon C., Salazar M. (2007a). Neuroendocrine disruption and health effects in Elliptio complanata mussels exposed to aeration lagoons for wastewater treatment. Chemosphere 68(4): 731-743.

Gagné F, Cejka P, André C, Hausler R, Blaise C. (2007b). Neurotoxicological effects of a primary and ozonated treated wastewater on freshwater mussels exposed to an experimental flow-through system. Comp Biochem Physiol C Toxicol Pharmacol. 146(4): 460-470.

Gagné F, André C, Gélinas M. (2010). Neurochemical effects of benzodiazepine and morphine on freshwater mussels. Comp Biochem Physiol C Toxicol Pharmacol. 152(2): 207-214.

Gezondheidsraad (2001). Advies Milieu-risico's van geneesmiddelen. Gezondheidsraad 2001/17.

Geudens PJJG. 2012. Drinkwaterstatistieken 2012 - de watercyclus van bron tot kraan. Vewin (Vereniging van waterbedrijven in Nederland), Rijswijk, the Netherlands.

Ginebreda A, Muñoz I, de Alda ML, Brix R, López-Doval J, Barceló D. (2010). Environmental risk assessment of pharmaceuticals in rivers: Relationships between hazard indexes and aquatic macroinvertebrate diversity indexes in the Llobregat River (NE Spain). Environment International 36(2):153-162.

Green, R.E., Taggart, M.A., Das, D., Pain, D.J., Sashi Kumar, C., Cunningham, A.A., Cuthbert, R., 2006. Collapse of Asian vulture populations: Risk of mortality from residues of the veterinary drug diclofenac in carcasses of treated cattle. Journal of Applied Ecology 43, 949-956.

Grontmij | AquaSense (2007) Onderzoek zandfiltratie rwzi Steenwijk: Onderzoek aan de verwijdering van metalen, geneesmiddelen en hormoonverstorende activiteit door zandfiltratie. In opdracht van waterschap Reest en Wieden. Rapportnummer 217755.

Grontmij | AquaSense (2008) Monitoring hormonen en geneesmiddelen: Analyses van effluent en oppervlaktewater. Rapport in opdracht van Waterschap de Dommel. Rapportnummer 239607.

Grontmij | AquaSense (2009) Onderzoek hormoonverstoorders en geneesmiddelen: rwzi Steenwijk, rwzi Echten en ziekenhuis Bethesda in Hoogeveen. Rapport in opdracht van waterschap Reest en Wieden. Rapportnummer 261572.

Grontmij (2011). Verbetering schatting effluentvrachten RWZI's. Aanbevelingen effluentvrachten voor EmissieRegistratie op basis van de Watson database. Grontmij, Amsterdam. Rapportnummer: 311275

Guler, Y. & A.T. Ford (2010). Anti-depressants make amphipods see the light. Aquat Toxicol. 99(3): 397-404.

Halling-Sørensen, B. (2000). Algal toxicity of antibacterial agents used in intensive farming. Chemosphere 40: 731-739.

Henry, T.B. & M.C. Black (2007). Mixture and single-substance acute toxicity of selective serotonin reuptake inhibitors in Ceriodaphnia dubia. Environ Toxicol Chem. 26(8): 1751-1755.

Heringa, M.B., Harmsen, D.J.H., Beerendonk, E.F., Reus, A.A., Krul, C.A.M., Metz, D.H., Ijpelaar, G.F., 2011. Formation and removal of genotoxic activity during UV/H2O2-GAC treatment of drinking water. Water Research In Press, Corrected Proof.

Hoeger B, Köllner B, Dietrich DR, Hitzfeld B. (2005). Water-borne diclofenac affects kidney and gill integrity and selected immune parameters in brown trout (Salmo trutta f. fario). Aquat Toxicol. 75(1):53-64.

Hofman-Caris, C.H.M., Beerendonk, E.F., 2011. New concepts of UV/H2O2 oxidation; KWR Watercycle Research Institute, Nieuwegein, the Netherlands.

Hofman-Caris, C.H.M., Harmsen, D.J.H., Wols, B.A., Janssen, L.J.J.M., Beerendonk, E.F., Knol, A.H., Hofman, J.A.M.H., 2011. Prediction of advanced oxidation performance in UV/H_2O_2 reactor systems with LP-UV lamps. pp. 460-467.

Holten Lützhøft, H.-C., B. Halling-Sørensen & S.E. Jørgensen (1999). Algal toxicity of antibacterial agents applied in Danish fish farming. Archives of Environmental Contamination and Toxicology 36: 1-6.

ICBR (2010). Bijlage bij ICBR-rapport 182, Evaluatierapport humane geneesmiddelen. Internationale Commissie ter Bescherming van de Rijn, Koblenz.

Isidori M., Nardelli A., Pascarella L., Rubino M., Parrella A. (2007). Toxic and genotoxic impact of fibrates and their photoproducts on non-target organisms. Environmental International 33:635-641.

Isidori, M., A. Parrella, P. Pistillo & F. Temussi (2009). Effects of ranitidine and its photoderivatives in the aquatic environment. Environ Int. 35(5): 821-825.

Jelic, A., Fatone, F., Di Fabio, S., Petrovic, M., Cecchi, F., Barcelo, D., 2012. Tracing pharmaceuticals in a municipal plant for integrated wastewater and organic solid waste treatment. Science of the Total Environment 433, 352-361.

Jonker, D., Freidig, A.P., Groten, J.P., De Hollander, A.E.M., Stierum, R.H., Woutersen, R.A., Feron, V.J., 2004. Safety evaluation of chemical mixtures and combinations of chemical and non-chemical stressors. Reviews on Environmental Health 19, 83-139.

Kahle M., Buerge I.J., Müller M.D. & Poiger T. (2009). Hydrophilic anthropogenic markers for quantification of wastewater contamination in ground- and surface waters. Environ Toxicol Chem. 28(12):2528-2536.

Kienle, C., Kase, R., Werner, I. 2011. Evaluation of bioassays and wastewater quality. In vitro and in vivo bioassays for the performance review in the Project "Strategy MicroPoll". Summary. Swiss Centre for Applied Ecotoxicology, Eawag-EPFL, Duebendorf.

Kiwa (2000), Mons M.N., J. van Genderen en A.M. van Dijk-Looijaard, Inventory on the presence of pharmaceuticals in Dutch water. Kiwa, Nieuwegein.

Kools, S.A.E., Boxall, A.B.A., Moltmann, J.F., Bryning, G., Koschorreck, J., Knacker, T., 2008. A ranking of European veterinary medicines based on environmental risks. Integrated Environmental Assessment and Management 4, 399-408.

Kormos J.L., M. Schulz, H.P. Kohler & T.A. Ternes (2010). Biotransformation of selected iodinated X-ray contrast media and characterization of microbial transformation pathways. Environ Sci Technol. 2010 Jul 1;44(13): 4998-5007.

Kotte, M., 2009. Evaluatie Screening RWS; aanbevelingen wat betreft gewasbeschermingsmiddelen en farmaceutica. Rijkswaterstaat WD, Lelystad, The Netherlands, p. 80.

Kümmerer, K., 2008. Pharmaceuticals in the Environment. Springer, Berlin, Germany.

Kümmerer, K., 2009. The presence of pharmaceuticals in the environment due to human use - present knowledge and future challenges. Journal of Environmental Management 90, 2354-2366.

Kuroda K., Murakami M., Oguma K., Muramatsu Y., Takada H. & Takizawa S. (2012). Assessment of groundwater pollution in Tokyo using PPCPs as sewage markers. Environ Sci Technol. 46(3):1455-1464.

Lange, H.J. de, W. Noordoven, A.J. Murk, M. Lürling & E.T. Peeters (2006). Behavioural responses of Gammarus pulex (Crustacea, Amphipoda) to low concentrations of pharmaceuticals. Aquat Toxicol. 78(3): 209-216.

Lange, F.T., Scheurer, M., Brauch, H.J., 2012. Artificial sweeteners-A recently recognized class of emerging environmental contaminants: A review. Analytical and Bioanalytical Chemistry 403, 2503-2518.

Larsson, D.G.J., de Pedro, C., Paxeus, N., 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. Journal of Hazardous Materials 148, 751-755.

Liu, Q.T., T.D. Williams, R.I. Cumming, G. Holm, M.J. Hetheridge & R. Murray-Smith (2009). Comparative aquatic toxicity of propranolol and its photodegraded mixtures: Algae and rotifer screening. Environmental Toxicology and Chemistry 28(12): 2622 - 2631.

Marsman et al., (2009). Aanwezigheid van geneesmiddelen, hormoonverstoorders en prioritaire stoffen in effluent en ontvangend oppervlaktewater. Waterschap Rivierenland, Tiel.

Martin-Diaz L, Franzellitti S, Buratti S, Valbonesi P, Capuzzo A, Fabbri E. (2009). Effects of environmental concentrations of the antiepilectic drug carbamazepine on biomarkers and cAMP-mediated cell signaling in the mussel Mytilus galloprovincialis. Aquat Toxicol. 94(3): 177-185.

Mehinto AC, Hill EM, Tyler CR. (2010). Uptake and biological effects of environmentally relevant concentrations of the nonsteroidal anti-inflammatory pharmaceutical diclofenac in rainbow trout (Oncorhynchus mykiss). Environ Sci Technol. 44(6): 2176-2182.

Mill, G.M.J. van, B.M. Verhoeven & G.B.J. Rijs (2006). Monitoring geneesmiddelen en oestrogenen 2005. Rapport Waterschap Aa en Maas/RIZA (Rijkswaterstaat).

Ministerie van Infrastructuur en Milieu (2011). Bestuursakkoord Water 2011-2015. Vereniging van Nederlandse Gemeenten (VNG), Interprovinciaal Overleg (IPO), Unie van Waterschappen (UvW) en Rijk .

Mons, M.N., Hoogenboom, A.C., Noij, T.H.M., 2003. Pharmaceuticals and drinking water supply in the Netherlands. KWR, Nieuwegein, the Netherlands, p. 76.

Monteiro, S.C., Boxall, A.B.A., 2010. Occurence and fate of human pharmaceuticals in the environment. Rev Environmental Contamination Toxicology, pp. 53-154.

Montforts, M.H.M.M., Rijs, G.B.J., Staeb, J.A., Schmitt, H., 2007. Diergeneesmiddelen en natuurlijke hormonen in oppervlaktewater van gebieden met intensieve veehouderij. RIVM, Bilthoven, The Netherlands, p. 70.

Montforts, M.H.M.M., van Rijswick, H.F.M.W., Freriks, A.A., Keessen, A.M., Wuijts, S., 2006. De relatie tussen productregistratie en waterkwaliteitsregelgeving: Geneesmiddelen, diergeneesmiddelen en veevoederalternatieven. RIVM, Bilthoven, The Netherlands, p. 145.

Montforts MHMM (2005). De drempelwaarden in de milieurisicobeoordeling voor (dier)geneesmiddelen in de Europese Unie: een kritische beschouwing. RIVM rapportnummer 601500002.

Montforts, M.H.M.M. (2006). Validation of the exposure assessment for veterinary medicinal products. Science of the Total Environment 358, 121-136.

Montforts MHMM, Keessen A (2008). Openbaarheid van milieu-informatie bij registratie van (dier) geneesmiddelen. RIVM rapportnummer 601500006.

Mulder, M., G. Notenboom, R. Lodder, J. Weijma, M. van Eekert and W. Moerman (2011). SOURCE. Simultaneous remOval of hUman and veteRinary pharmaCeuticals and nutriEnts. Eindrapportage. Lettinga Associates Foundation for environmental protection and resource conservation, Wageningen.

Müller C, Ruby S, Brousseau P, Cyr D, Fournier M, Gagné F. (2009). Immunotoxicological effects of an activated-sludge-treated effluent on rainbow trout (Oncorhynchus mykiss). Comp Biochem Physiol C Toxicol Pharmacol. 150(3): 390-394.

Nakada, N., K. Kiri, H. Shinohara, A. Harada, K. Kuroda, S. Takizawa, & H. Takada (2008). Evaluation of Pharmaceuticals and Personal Care Products as Water-soluble Molecular Markers of Sewage. Environ. Sci.Tech. 42:6387-6353.

Nassef M, Matsumoto S, Seki M, Khalil F, Kang IJ, Shimasaki Y, Oshima Y, Honjo T. (2010). Acute effects of triclosan, diclofenac and carbamazepine on feeding performance of Japanese medaka fish (Oryzias latipes). Chemosphere. 80(9): 1095-1100.

NORMAN (2009). NORMAN Working Group on Prioritisation of emerging substances. WG Mandate and Workplan for 2009. April 2009. www.norman-network.com, working groups, WG1 Priorisation.

Oosterhuis, M., Groteboer, A., van der Wiele, P.J., 2011. Emissie geneesmiddelen bij de bron aanpakken. H2O, 30-33.

Oranjewoud (1999). Effecten van cytostatica in afvalwater. Documentnr. 843-10. In opdracht van Pharmachemie.

Ort, C., Lawrence, M.G., Reungoat, J., Mueller, J.F., 2010. Sampling for PPCPs in Wastewater Systems: Comparison of Different Sampling Modes and Optimization Strategies. Environmental Science & Technology 44, 6289-6296

Painter, M.M., M.A. Buerkley, M.L. Julius, A.M. Vajda, D.O. Norris, L.B. Barber, E.T. Furlong, M.M. Schultz & H.L. Schoenfuss (2009). Antidepressants at environmentally relevant concentrations affect predator avoidance behavior of larval fathead minnows (Pimephales promelas). Environ Toxicol Chem. 28(12): 2677-2684.

Pérez S, Barceló D. (2007). Fate and occurrence of X-ray contrast media in the environment. Anal Bioanal Chem. 2007 Feb;387(4):1235-46.

Petrovic, M., De Alda, M.J.L., Diaz-Cruz, S., Postigo, C., Radjenovic, J., Gros, M., Barcelo, D., 2009. Fate and removal of pharmaceuticals and illicit drugs in conventional and membrane bioreactor wastewater treatment plants and by riverbank filtration. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences 367, 3979-4003.

Pomati, F., S. Castiglioni, E. Zuccato, R. Fanelli, D. Vigetti, C. Rossetti & D. Calamari (2006). Effects of a complex mixture of therapeutic drugs at environmental levels on human embryonic cells. Environ Sci Technol. 40(7):2442-2447.

Pomati, F., C.J. Cotsapas, S. Castiglioni, E. Zuccato E & D. Calamari D. (2007). Gene expression profiles in zebrafish (Danio rerio) liver cells exposed to a mixture of pharmaceuticals at environmentally relevant concentrations. Chemosphere 70(1):65-73.

Pomati, F., C. Orlandi, M. Clerici, F. Luciani & E. Zuccato (2008). Effects and Interactions in an Environmentally Relevant Mixture of Pharmaceuticals. Toxicological Sciences 102(1): 129-137.

Quinn B, Gagné F & Blaise C. (2009). Evaluation of the acute, chronic and teratogenic effects of a mixture of eleven pharmaceuticals on the cnidarian, Hydra attenuata. Sci Total Environ. 407(3): 1072-1079.

Radjenovic, J., Petrovic, M., Barcelo, D., 2007. Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. Analytical and Bioanalytical Chemistry 387, 1365-1377.

Radjenovic, J., Petrovic, M., Ventura, F., Barcelo, D., 2008. Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment. Water Research 42, 3601-3610.

RadjenoviβJ, PetroviβM, Barceló D. 2009. Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment. Water Res. Feb;43(3):831-41.

Reddersen, K., Heberer, T., Dunnbier, U., 2002. Identification and significance of phenazone drugs and their metabolites in ground- and drinking water. Chemosphere 49, 539-544.

Reungoat J, Macova M, Escher BI, Carswell S, Mueller JF, Keller J. (2010). Removal of micropollutants and reduction of biological activity in a full scale reclamation plant using ozonation and activated carbon filtration. Water Res. 44(2): 625-637.

RIWA, 2009. Stroomgebiedsbeheersplan voor het internationale district van de Maas - Overkoepelend deel. RIWA Maas, Liege, Belgium.

RIWA, 2011a. Jaarrapport 2010 De Rijn. RIWA Rijn, Nieuwegein, p. 216.

RIWA, 2011b. Jaarrapport 2010 Maas. RIWA, p. 56.

RIWA/RIZA (2001). Milieu-effecten van humane geneesmiddelen. Aanwezigheid en risico's. In opdracht van Samenwerkende Rijn- en Maaswaterleidingbedrijven (RIWA), Amsterdam en Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling (RIZA), Lelystad. RIZA-rapportnummer 2001.051

RIZA (2006a). Risicovolle lozingen op de Maas. Onderzoek naar het voorkomen en effect van geloosde risicovolle stoffen (waaronder KRW-stoffen) op de Maas door rioolwaterzuiveringen en industriële afvalwaterzuiveringen in het beheersgebied van RWS-Limburg. RIZA rapport 2006.014. RIZA, Lelystad.

RIZA (2006b). Risicovolle lozingen op de Maas - deel 2. Onderzoek naar het voorkomen en effect van geloosde risicovolle stoffen (waaronder KRW-stoffen) op de Maas door rioolwaterzuiveringen en industriële afvalwaterzuiveringen in het beheersgebied van RWS-Limburg. Resultaten van aanvullende metingen. Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling (RIZA), Lelystad. RIZA rapportnummer 2006.032. Aanvulling op RIZA rapport 2006.014.

Roessink, I., G. Fait, J.D.M. Belgers en M.C. Boerwinkel, 2012. Mogelijke effecten van geneesmiddelen in effluent op aquatische organismen. Alterra, Wageningen. Alterra-rapport 2338.

Roig, B., 2010. Pharmaceuticals in the environment - Current knowledge and need assessment to reduce presence and impact. IWA, London, UK, p. 198.

Roorda J.H. & J.G.M. Derksen (2006). Emissiereductie van humane geneesmiddelen naar watermilieu. Advies aan de LBOW-werkgroep '(dier)geneesmiddelen en watermilieu'. In opdracht van het Ministerie van Volksgezond, Ruimtelijke Ordening en milieu (VROM). Grontmij, De Bilt. Grontmij rapportnummer 99053802.

Roos, V., L. Gunnarsson, J. Fick, D.G. Larsson & C. Rudén (2012). Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. Sci Total Environ. 421-422: 102-110.

Sadezky, A., D. Löffler & T. Ternes (2008). KNAPPE Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. Deliverable D1.2: Proposal of an environmental indicator and classification system of pharmaceutical product residues for environmental management. Http://www.knappe-eu.org

Sacher, F. en P. Stoks (2003), Pharmaceutical residues in waters in the Netherlands RIWA, Nieuwegein. www.riwa.org 31-05-2007.

Salo HM, Hébert N, Dautremepuits C, Cejka P, Cyr DG, Fournier M. (2007). Effects of Montreal municipal sewage effluents on immune responses of juvenile female rainbow trout (Oncorhynchus mykiss). Aquatic Toxicology 84(4): 406-414.

Scheurer M., Storck F.R., Graf C., Brauch H.J., Ruck W., Lev O. & Lange F.T. (2011). Correlation of six anthropogenic markers in wastewater, surface water, bank filtrate, and soil aquifer treatment. J Environ Monit. 13(4):966-973.

Scheurer, M., Michel, A., Brauch, H.-J., Ruck, W., Sacher, F., 2012. Occurrence and fate of the antidiabetic drug metformin and its metabolite guanylurea in the environment and during drinking water treatment. Water Research 46, 4790-4802.

Scheurer, M., Sacher, F., Brauch, H.-J., 2009. Occurence of the antidiabetic drug metformin in sewage and surface waters in Germany. Journal of Environmental Monitoring 11, 1608-1613.

Schmitt H., T. Boucard, J. Garric, J. Jensen, J. Parrott, A. Péry, J. Römbke, J.O. Straub, T.H. Hutchinson, P. Sánchez-Arguëllo, A. Wennmalm & K. Duis (2010). Recommendations on the environmental risk assessment of pharmaceuticals: Effect characterization. Integrated Environmental Assessment and Management 6(1): 588–602.

Schrap, S.M., Rijs, G.B.J., Beek, M.A., Maaskant, J.F.N., Staeb, J., Stroomberg, G., Tiesnitsch, J., 2003. Human and veterinary pharmaceuticals in Dutch surface waters and waste waters. "Humane en veterinaire geneesmiddelen in Nederlands oppervlaktewater en afvalwater". Dutch Institute for Inland Water Management and Waste Water Treatment (RIZA), Lelystad, the Netherlands, p. 86.

Schriks, M., Heringa, M.B., Kooi, V.D., De Voogt, P., Van Wezel, A.P., 2010. Toxicological relevance of emerging contaminants for drinking water quality. Water Research 44, 461-476.

Schwaiger J, Ferling H, Mallow U, Wintermayr H, Negele RD. (2004). Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part I: histopathological alterations and bioaccumulation in rainbow trout. Aquat Toxicol. 68(2): 141-150.

Schulze, T., S. Weiss, E. Schymanski, P.C. von der Ohe, M. Schmitt-Jansen, R. Altenburger, G. Streck & W. Brack (2010). Identification of a phytotoxic photo-transformation product of diclofenac using effect-directed analysis. Environmental Pollution 158(5): 1461-1466.

Schulz M, Löffler D, Wagner M, Ternes TA. (2008). Transformation of the X-ray Contrast Medium Iopromide In Soil and Biological Wastewater Treatment. Environ. Sci. Technol., 2008, 42 (19), pp 7207–7217.

Sebire M, Allen Y, Bersuder P, Katsiadaki I. (2008). The model anti-androgen flutamide suppresses the expression of typical male stickleback reproductive behaviour. Aquat Toxicol. 90(1):37-47.

Snijdelaar, M., C. Leijen, J. Lambers en T. Brandwijk (2006). Problematiek rond diergeneesmiddelen in oppervlaktewater. LNV-Directie Kennis, rapportnr. 2006/060.

SPGE, 2006. PASH Plan dássainissement par sous-bassin hydrographique; sous-bassin de la Meuse Aval. Société Publique de Geistion de l'Eau.

Stalter D., Magdeburg A., Wagner M., Oehlmann J. (2011). Ozonation and activated carbon treatment of sewage effluents: removal of endocrine activity and cytotoxicity. Water Res. 45(3): 1015-1024.

Stalter D., Magdeburg A., Weil M., Knacker T., Oehlmann J. (2010). Toxication or detoxication? In vivo toxicity assessment of ozonation as advanced wastewater treatment with the rainbow trout. Water Res. 44(2): 439-448.

Stanley JK, Ramirez AJ, Chambliss CK, Brooks BW. (2007). Enantiospecific sublethal effects of the antidepressant fluoxetine to a model aquatic vertebrate and invertebrate. Chemosphere 69(1):9-16.

STOWA (2003). Review oestrogenen en geneesmiddelen in het milieu. Stand van zaken en kennislacunes. In opdracht van Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2003-09.

STOWA (2006). Onderzoek MBR Varsseveld. Deelstudie verwijdering bijzondere stoffen. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2006-06.

STOWA, (2007a). Verg(h)ulde Pillen. Deel A Bureaustudie. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2007-03.

STOWA (2007b). Effluentnabehandeling op rwzi Maasbommel. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2007-17

STOWA (2007c). Ervaringen met nageschakelde MBR op rwzi Leeuwarden. Verwijdering van hormoonverstorende stoffen, geneesmiddelen en andere microverontreinigingen. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2007-23

STOWA (2008). Verkenning geneesmiddelen en toxiciteit effluent rwzi's. Gecombineerd onderzoek, bioassays en chemie. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2008-06.

STOWA (2009a). Verg(h)ulde pillen, eindrapport deel B. Case studies bij het Refaja Ziekenhuis te Stadskanaal, het St. Anthoniusziekenhuis te Nieuwegein en het Leids Universitair Medisch Centrum. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Utrecht. STOWA rapport 2009-06 en bijbehorende werkrapporten 2009-W01 t/m W03 (3 individuele rapporten).

STOWA (2009b) Nageschakelde zuiveringstechnieken op de awzi Leiden Zuid-West. Verkenning actiefkooladsorptie en geavanceerde oxidatietechnieken. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2009-33.

STOWA (2009c) 1 Step filter als effluentpolishingstechniek. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2009-34.

STOWA (2009d). Monitoringsdata van KRW en E-PRTR stoffen in effluenten. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2009-30.

STOWA (2010a). ZORG. Zoeken naar Oplossingen voor Reductie van Geneesmiddelen emissies uit zorginstellingen. Deel A. Bureaustudie. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2010-06.

STOWA (2010b). Actievekoolfiltratie op afloop nabezinkank. Demonstratieonderzoek op vier rwzi's. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2010-27.

STOWA (2011a). Gebiedstudie geneesmiddelen provincie Utrecht. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2011-09.

STOWA (2011b). ZORG. Deel B . Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2011-W01 t/m W08 (8 individuele rapporten).

STOWA (2011c). Inventarisatie van emissie van geneesmiddelen uit zorginstellingen. ZORG, Deel C. Stichting Toegepast Onderzoek Waterbeheer (STOWA), Amersfoort. STOWA rapport 2011-02

ter Laak, T.L., Hofman, J., in prep. Geneesmiddelen in de Watercyclus in Limburg. KWR, Watercycle Research Institute, Nieuwegein, The Netherlands.

ter Laak, T.L., Hofs, B., De Jongh, C.M., Wols, B., Hofman-Caris, R., 2011a. Selecting relevant pharmaceuticals for monitoring, risk assessment and removal studies, version 1. KWR Watercycle Reserach Institute, Nieuwegein, the Netherlands, p. 33.

ter Laak, T.L., Kolkman, A., Heuvel, H., Kotte, M., 2011b. Evaluatie screening RWS (2010). RWS, KWR, Lelystad, The Netherlands, p. 51.

ter Laak, T.L., Puijker, L.M., van Leerdam, J.A., Raat, K.J., de Voogt, P., van Wezel, A.P., 2012. Broad screening of organic chemicals in Dutch groundwater and their occurrence in relation to land use and hydrology. Science of the Total Environment, 308-313.

ter Laak, T.L., van der Aa, M., Houtman, C., Stoks, P., van Wezel, A., 2010. Temporal and spatial trends of pharmaceuticals in the Rhine. Association of River Waterworks, RIWA, Nieuwegein, the Netherlands, p. 44.

Ternes (2012). Transformation product: New emerging contaminants of the urban water cycle. Presentation at the NORMAN Workshop "Sampling and Analysis of Emerging Contaminants in the Aquatic Environment: Current and future challenges", 1-2 March 2012 in Oslo, Norway.

TGD-EQS (2011). Common Implementation Strategy for the Water Framework Directive (2011). Guidance document No 27. Technical Guidance for Deriving Environmental Quality Standards.

Trautwein, C., Kümmerer, K., 2011. Incomplete aerobic degradation of the antidiabetic drug Metformin and identification of the bacterial dead-end transformation product Guanylurea. Chemosphere 85, 765-773.

Triebskorn R, Casper H, Heyd A, Eikemper R, Köhler HR, Schwaiger J. (2004). Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part II: cytological effects in liver, kidney, gills and intestine of rainbow trout (Oncorhynchus mykiss). Aquat Toxicol. 68(2): 151-166.

Triebskorn R, Casper H, Scheil V, Schwaiger J. (2007). Ultrastructural effects of pharmaceuticals (carbamazepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss) and common carp (Cyprinus carpio). Anal Bioanal Chem. 387(4): 1405-1416.

Tweede Kamer (2007). Brief van de staatssecretaris van VROM over voorgenomen en deels al in gang gezette acties gericht op het reduceren van de s van oppervlaktewater en grondwater met humane en veterinaire geneesmiddelen. Tweede Kamer, vergaderjaar 2006-2007, 28 808, nr. 39.

Tweede Kamer (2009). Beknopte voortgangsrapportage Uitvoeringsprogramma Diffuse Bronnen Waterverontreiniging inclusief geneesmiddelen. Brief van de staatssecretaris van VROM, 30 september 2009. Kenmerkt DP/2009054989.

van der Aa, N.G.F.M., Kommer, G.J., de Groot, G.M., Versteegh, J.F.M., 2008. Geneesmiddelen in bronnen voor drinkwater. Monitoring, toekomstig gebruik en beleidsmaatregelen. RIVM, Bilthoven, p. 61.

van der Aa, N.D., E, Bijlsma, L., Emke, E., van de Ven, B., van Nuijs, A., de Voogt, P., 2011a. Drugs of abuse and tranquilizers in Dutch surface waters, drinking water and wastewater : Results of screening monitoring 2009 RIVM, Bilthoven, p. 92.

van der Aa, N.G.F.M., Kommer, G.J., van Montfoort, J.E., Versteegh, J.F.M., 2011b. Demographic projections of future pharmaceutical consumption in the Netherlands. Water Science and Technology, 825-832.

van der Aa, N.G.F.M., van Vlaardingen, P.L.A., van leeuwen, L.C., Post, M., 2011c. Assessment of potential risks of 11 pharmaceuticals for the environment. Using environmental information from public databases RIVM, Bilthoven, The Netherlands, p. 30.

van der Kooij, D., van Genderen, J., Heringa, M.B., Hogenboom, A.C., de Hoogh, C., Mons, M.N., Puijker, L., Slaats, N., Vreeburg, J., van Wezel, A.P., 2010. Drinkwaterkwaliteit Q21. KWR, Watercycle Research Institute, Nieuwegein, the Netherlands, p. 155.

Verlicchi, P., Al Aukidy, M., Zambello, E., 2012. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment-A review. Science of the Total Environment 429, 123-155.

Verliefde, A.R.D., 2008. Rejection of organic micropollutants by high pressure membranes (NF/RO). Technical University Delft, p. 281.

Versteegh, J.F.M., Stolker, A.A.M., Niesing, W., Muller, J.J.A., 2003. Geneesmiddelen in drinkwater en drinkwaterbronnen. Resultaten van het meetprogramma 2002. Bilthoven, the Netherlands, p. 45.

Versteegh, J.F.M., Van der Aa, N.G.F.M., Dijkman, E., 2007. Geneesmiddelen in drinkwater en drinkwaterbronnen. Resultaten van het meetprogramma 2005/2006. RIVM, Bilthoven, p. 53.

Walraven, N., Laane, R.W.P.M., 2009. Assessing the discharge of pharmaceuticals along the Dutch coast of the North Sea. Rev Environmental Contamination Toxicology 199, 1-18.

Webb, S.F. (2001). A data-based perspective on the environmental risk assessment of human pharmaceuticals I – collation of available ecotoxicity data. In: K. Kümmerer (ed.). Pharmaceuticals in the environment. Sources, fate, effects and risks. Universitatsklinikum Freiburg. Springer, Heidelberg. p175-201.

WHO, 2011. Pharmaceuticals in drinking-water. World Health Organization, Geneva, Switzerland, p. 35.

Wirtz F. 2009. Danube, Meuse and Rhine MEMORANDUM 2008. Environmental science and pollution research international 16 Suppl 1:S112-115.

Wols, B.A., Hofman-Caris, C.H.M., 2012. Review of photochemical reaction constants of organic micropollutants required for UV advanced oxidation processes in water. Wat. Res. 46, 2815-2827.

Wols, B.A., Hofman, J.A.M.H., Beerendonk, E.F., Uijttewaal, W.S.J., van Dijk, J.C., 2011. A systematic approach for the design of UV reactors using CFD. AIChE Journal 57, 193-207.

Wols, B.A., Vries, D., 2011. On a QSAR approach for the prediction of priority compound degradation by water treatment processes. International Water Week, Amsterdam, The Netherlands.

ANNEX 1

A HISTORICAL PERSPECTIVE ON PHARMACEUTICALS: FROM EMERGING SUBSTANCES TO EMISSION REDUCTION MEASURES

Along the path from emerging substances to emission reduction measures, four phases can be distinguished:

1 Signalling "emerging" problem substances
Since 2000, a variety of exploratory literature studies on the presence and risks of pharmaceuticals have been conducted (Kiwa, 2000; RIWA/RIZA, 2001; Gezondheidsraad, 2001; STOWA, 2003). In 2003, RIZA, Kiwa, RIWA and RIVM published the results of collective research into the presence of pharmaceuticals in drinking water, process water, surface water and wastewater (Mons et al., 2003; Schrap et al., 2003; Versteegh et al., 2003, Sacher en Stoks, 2003). Moreover, research focused on the presence of veterinary pharmaceuticals (and hormones) in cattle breeding areas (Montforts et al., 2007).

2 Stakeholder attention
The research results motivated the establishment of an interdepartmental working group – "Emission-reduction of human and veterinary pharmaceuticals" – comprising representatives from the ministries of Housing, Spatial Planning and the Environment, Transport, Public Works and Water Management, and Health, Welfare and Sport, as well as RIZA, RIWA, Vewin and RIVM.[12] The working group reports to the National Administrative Consultation Committee on Water (LBOW) and its objective is to "minimise the environmental impact of the use of human and veterinary pharmaceuticals."

In 2005, the working group commissioned a chain analysis, which included an inventory of possible emission reduction measures (Derksen and Roorda, 2005). This was followed by a more detailed study of the feasibility of the highest-potential measures for human pharmaceuticals (Roorda en Derksen, 2006) and veterinary pharmaceuticals (Snijdelaar et al., 2006). The studies' results were used as input to the working group's Policy Letter. In February 2007, the State Secretary sent this Policy Letter (VROM, 2007) to the Lower House, where planned and already-initiated actions on emission reduction were elaborated. These included actions to promote environmentally-friendly pharmaceuticals (Green Pharmacy), and targeted pharmaceutical use (electronic patient record). These actions have positive environmental effects over the long term. Other actions focus on research into pharmaceutical emissions from various sources and end-of-pipe treatment techniques for pharmaceutical removal. Although these techniques are still in their early infancy when it comes to implementation in

12 This working group is currently dormant.

(city) wastewater, there are other techniques available that are implementable and can have a positive environmental impact, even in the medium term, according to the 2009 progress report to the Lower House (Tweede Kamer, 2009).

3 Supplementary studies/filling knowledge gaps

Studies have been carried out in three areas with the aim of filling knowledge gaps:

- Studies into the contributions of hospitals, healthcare institutions and residential areas
- (STOWA, 2009a; STOWA 2011c). These studies have supplied the emission data that permit the calculation of the relative contributions. In a couple of area studies (STOWA, 2011b; ter Laak en Hofman, in prep.) these emission data were used to determine hotspots.
- Studies into additional treatment techniques, including activated carbon, oxidation and filtration (STOWA, 2010b; 2009b, c; 2007b, c; 2006; Grontmij|AquaSense, 2007).
- Studies into new sanitation concepts, including urine-separation and Pharmafilter (an integral concept for hospital waste and wastewater). For a project overview see http://nieuwesanitatie.stowa.nl.

4 Policy elaboration/preparation

The results of the Policy Letter actions and of the supplementary studies motivated the Ministry of Infrastructure and the Environment (I&M) to proceed with research into how and where in the wastewater treatment chain the wastewater could be treated with a view to reducing the load of human pharmaceuticals on the aquatic environment. Also, explorations were carried out into how these measures could be financed. The report has been completed (Grontmij, 2011a) and will serve as input to a new Policy Letter to be presented to the Lower House in the second half of 2012.

ANNEX 2

ENVIRONMENTAL ASSESSMENT IN THE PHARMACEUTICAL APPROVAL PROCESS

The EU Directive 2001/83/EC (EC, 2001), modified in Directive 2004/27/EC (EC, 2004), establishes that only registered and approved pharmaceuticals can be used. This registration can be carried out centrally at the European Medicines Agency (EMA), or for each country separately. In the Netherlands, it is the Medicines Evaluation Board (CBG) that is responsible for the group of pharmaceuticals available.

The registration procedure for human pharmaceuticals also requires that an environmental assessment be carried out. The details of how this assessment is to be conducted are laid out in the EMEA "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006a; modified in EMEA, 2006b). The first step in the risk assessment involves a calculation of the worst-case concentration, which is compared to a threshold value (0.01µg/L). This threshold value is not scientifically-founded and should actually be set lower (Montforts, 2005; Schmitt et al., 2010). If the threshold value is exceeded, or if effects on reproduction are expected at lower concentrations (for example, through hormone disrupting properties), a more extensive, phase-2 risk assessment is necessary. In this phase, the predicted environmental concentrations are refined and compared with Predicted No Effect Concentrations. A possible environmental risk, however, cannot constitute grounds for the refusal of a substance's approval, because of the major importance of pharmaceuticals to public health. Nor is there any obligation to monitor a substance's presence and effects on the environment after it has received approval (Montforts et al., 2006).

There has been a call to make the information from the environmental assessment public upon the pharmaceutical's registration (Montforts & Keessen, 2008). The European Medicines Agency (EMA) has recently agreed that, following a pharmaceutical's EU-wide registration and approval, a table containing all the results (endpoints) of the environmental component of the registration dossier should be included in the European Public Assessment Report (EPAR) that is posted on the EMA website (www.ema.europa.eu). For pharmaceuticals registered and authorised in the Netherlands, the Medicines Evaluation Board can post a summary of the environmental studies in the Medicines Data Bank on www.cbgmeb.nl. However, in the spring of 2012, no environmental information had yet been made available on either site (van der Aa et al., 2011b).

ANNEX 3

ATC MAIN GROUPS

ATC code (according to http://www.whocc.no/atc_ddd_index/), main group indication (first letter)

A Alimentary tract and metabolism
B Blood and blood forming organs
C Cardiovascular system
D Dermatologicals
G Genitourinary system and sex hormones
H Systemic hormonal preparations, excluding sex hormones and insulins
J Antiinfectives for systemic use
L Antineoplastic and immunomodulating agents
M Musculo-skeletal system
N Nervous system
P Antiparasitic products, insecticides and repellents
Q Veterinary medicines
R Respiratory system
S Sensory organs
V Various

ANNEX 4

MONITORING RESULTS (RANGES)

Substance description	n	concentration range (µgL)	References
Amidotrizoine acid /diatrizoate (X-ray constrast medium)			
WWTP effluent	8	<0.05 - 0.100	Grontmij|AquaSense, 2008a
surface water: large rivers	171	0.02 – 0.75	ter Laak and Hofman, in prep., REWAB database 2010***, RIWA database 2011*****
surface water: regional	24	<0.01 - 0.44	ter Laak and Hofman, in prep., Grontmij|AquaSense, 2008a
groundwater and bank-filtration water	5	<0.01	De Jongh et al., 2012
drinking water	52	<0.01 - 0.09	REWAB database 2010
Carbamazepine (antiepileptic)			
WWTP effluent	46	0.23 - 1.5****	STOWA, 2011a; Grontmij|AquaSense, 2008a; STOWA, 2006: Schrap et al. 200; STOWA, 2011b
surface water: large rivers	246	<0.005 - 0.3	ter Laak and Hofman, in prep., Versteegh et al., 2007, RIWA database 2011*****
surface water: regional	36	0.01 - 0.54	STOWA, 2011a; Grontmij|AquaSense, 2008a; ter Laak and Hofman, in prep.
groundwater and bank-filtration water	29	0.01 - 0.083	De Jongh et al.,2012, Versteegh et al., 2007
drinking water	42	<0.01 – 0.025	Versteegh et al., 2007
Diclofenac (painkiller)			
WWTP effluent	60	<0.01 - 0.89	Schrap et al., 2003; STOWA, 2006; STOWA, 2009; STOWA, 2011a; STOWA, 2011b; Grontmij|AquaSense, 2007; Grontmij|AquaSense, 2008a,
surface water: large rivers	232	<0.0004 - 0.18	ter Laak and Hofman, in prep. Versteegh et al.,2007***, REWAB database 2010*** RIWA database 2011*****
surface water: regional	54	<0.01 - 0.70	Schrap et al., 2003; STOWA, 2011a; ter Laak and Hofman, in prep. Grontmij|AquaSense, 2008a
groundwater and bank-filtration water	155	<0.01 - 0.012	REWAB database 2010, De Jongh et al., 2012, Versteegh et al., 2007
drinking water	155	<0.01** - 0.018	REWAB database 2010, Versteegh et al.,2007
Metformin (antidiabetic)			
WWTP effluent	34	0.71 - 27.5	STOWA, 2011a; STOWA, 2011b; unpublished results waterschap Regge & Dinkel, 2011
surface water: large rivers	43	0.07 - 4.2	ter Laak and Hofman, in prep. RIWA database 2011*****
surface water: regional	32	0.4 – 6.4	STOWA, 2011a, ter Laak and Hofman, in prep.
groundwater and bank-filtration water	13	<0.05	Unpublished results, KWR
drinking water	6	<0.05	Unpublished results, KWR

Metoprolol (β-blocker)

WWTP effluent	46	0.32 - 3.2	STOWA, 2011a; Grontmij|AquaSense, 2008a; STOWA, 2006; Schrap et al., 2003; STOWA, 2011b
surface water: large rivers	196	<0.005 - 0.29	ter Laak and Hofman, in prep. Versteegh et al., 2007***, REWAB database 2010***, RIWA database 2011*****
surface water: regional	36	<0.01 - 1.2*	STOWA, 2011a; Grontmij|AquaSense, 2008a; ter Laak and Hofman, in prep.
groundwater and bank-filtration water	29	<0.01	De Jongh et al., 2012, Versteegh et al., 2007 drinking water
drinking water	91	<0.06 – 0.026	REWAB database 2010, Versteegh et al., 2007

Sulfamethoxazole (antibiotic)

WWTP effluent	46	<0.01 - 0.35	STOWA, 2011a; Grontmij|AquaSense, 2008a; STOWA, 2006; Schrap et al., 2003; STOWA, 2011b
surface water: large rivers	306	<0.004 - 0.16	ter Laak and Hofman, in prep., Versteeg et al.,2007***, REWAB database 2010***, RIWA database 2011*****
surface water: regional	36	0.01 - 0.20*	STOWA, 2011a; Grontmij|AquaSense, 2008a;
ter Laak and Hofman, in prep. groundwater and bank-filtration water	56	<0.01 – 0.014	Versteeg et al.,2007
drinking water	90	<0.01 – 0.025	REWAB database 2010, Versteeg et al.,2007

* Traces also found below the detection limit, so that the detection limit was higher than the given value.

** Detection limit in REWAB database was occasionally 0.02 µg/L.

*** Concerns water drawn from the Meuse and Rhine basins for the production of drinking water.

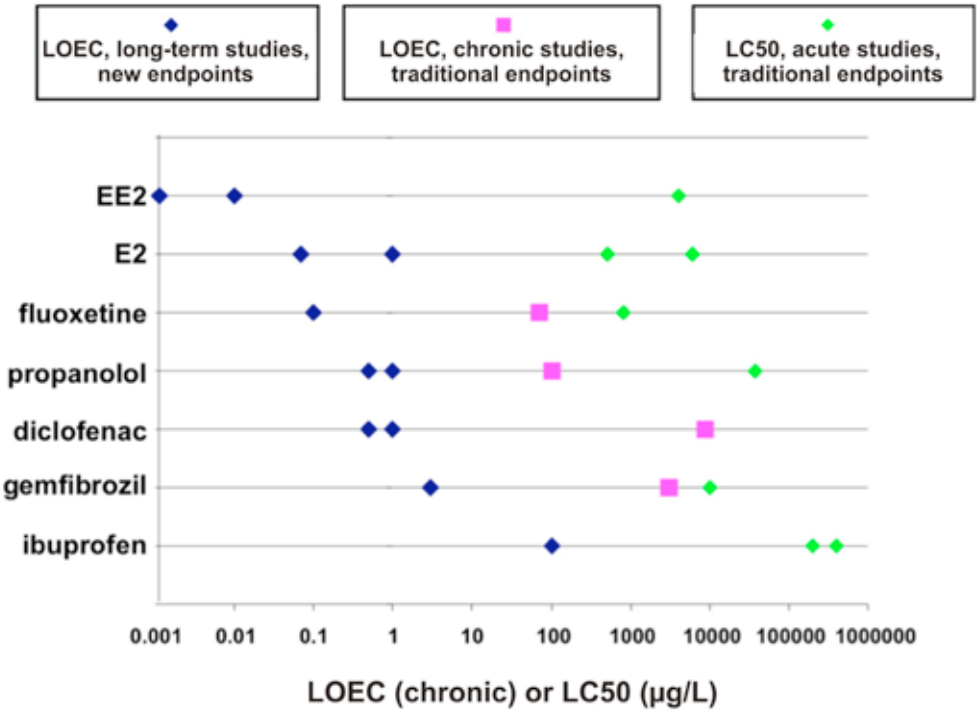
**** In STOWA (2011b) a single peak at 13 µg/L.

***** Concerns water from the Meuse, Rhine and Drenthe Aa basins near drinking water intake points and on the borders with Belgium and Germany.

ANNEX 5

TRADITIONAL SAFETY FACTORS IN RISK ASSESSMENTS PROVIDE INSUFFICIENT PROTECTION FROM PHARMACEUTICALS WITH SPECIFIC EFFECTS

FIGURE 1 COMPARISON OF EFFECT CONCENTRATIONS FOR ACUTE, CHRONIC AND SPECIFIC TOXICITY. LOEC = LOWEST OBSERVED EFFECT CONCENTRATION, I.E., THE LOWEST CONCENTRATION AT WHICH AN EFFECT IS STILL MEASURED. LC50 = THE LETHAL CONCENTRATION AT WHICH 50% OF LABORATORY ANIMALS DIE. SOURCE: BOXALL ET AL. (2008).



When risk assessments of substances are conducted, a risk estimate is made on the basis of a comparison between, on the one hand, the substance's concentration and, on the other, its toxicity. This risk estimate is expressed in the PEC/PNEC ratio. The concentration is expressed in the Predicted Environmental Concentration (PEC), which is measured or calculated. While the toxicity is expressed in a Predicted No Effect Concentration (PNEC), which is derived from laboratory toxicity tests. A PEC/PNEC ratio greater than 1 means that a risk exists.

Safety factors are typically applied to correct for uncertainties. The correction factors vary from 10 to 1,000, based on:

- Acute/chronic ratio = 10
- Differences between species = 10
- Differences between laboratory and field = 10

For specific active substances, such as pharmaceuticals or hormones, these correction factors do not always provide sufficient protection (Boxall et al., 2008; Ankley et al., 2005.: Cunningham et al., 2006). Figure 1 shows the acute, chronic and specific effects of a few pharmaceuticals. For illustration purposes, the figure also contains information on the hormones ethinyloestradiol (EE2, "the pill") and oestradiol (E2). The difference between acute mortality and specific effects (such as hormone disruption, or on behaviour or activity) is more than 1,000 for all the pharmaceuticals presented and, for fluoxetine and propanolol, even much more.

ANNEX 6

PROVISIONAL STANDARDS AND PNEC VALUES FOR SURFACE WATER

PROVISIONAL STANDARDS FOR DICLOFENAC AND ETHINYLOESTRADIOL IN THE WATER FRAMEWORK DIRECTIVE

On 31 January 2012, the revised list of WFD priority substances was published, see http://europa.eu/rapid/pressReleasesAction.do?reference=IP/12/88 and http://ec.europa.eu/environment/water/waterdangersub/lib_pri_substances. htm#prop_2011_docs. Among the new priority substances proposed are two pharmaceuticals: namely, the painkiller diclofenac and 7 alpha-ethinyloestradiol, the active ingredient in the contraceptive pill.[13]

The proposed standard (A AEQS) is 0.1 µg/L for diclofenac and 0.035 ng/L for ethinyloestradiol. This standard applies to annual averages in inland surface waters, that is, rivers, lakes and related artificial or significantly altered water bodies. For other surface waters (i.e., marine waters) the proposed standard for diclofenac is ten times lower, that is, 0.01 µg/L, and five times lower for ethinyloestradiol, that is, 0.007 ng/L .
The standards were derived according to the system contained in the European Technical Guidance Document (TGDEQS, 2011), which takes account of specific effects (kidney damage for diclofenac, hormonal effects for ethinyloestradiol).
If everything runs according to plan, this standard will be obligatory in 2021, with the implementation of the second river basin management plan. Exceptions will however be possible for special cases.

PROVISIONAL PNEC VALUES

Van der Aa et al. (2011c) derived provisional Predicted No Effect Concentrations for 11 pharmaceuticals: namely, diclofenac, metformin, paracetamol, amoxicillin, irbesartan, carbamazepine, fluoxetine, furosemide, ofloxacin, sulfamethoxazole, trimethoprim and valsartan. The PNECs are based on data from the Swedish SECIS system (see "Swedish PNEC Values" below). The derivation took the lowest value per taxonomic group, and then applied the ECHA (2008) correction factors. These correction factors were also used for REACH (industrial substances), biocides and in setting the European standards in the Water Framework Directive. The derived PNEC standards vary significantly, from 0.026 µg/L for the antibiotic ofloxacin to 320000 µg/L for the diuretic furosemide.

SWEDISH PNEC VALUES

In Sweden, the ecotoxicity data on pharmaceuticals have been collected for quite a long time within the framework of the Swedish Environmental Classification and Information System (SECIS). This is a voluntary system that is kept updated by the Swedish Association for the Pharmaceutical Industry (LIF) and supported by various health-sector stakeholders (Ågerstrand and Rudén, 2010). The data are used for risk assessments, which can be accessed on http://www.fass.se/LIF/miljo/miljoinfo.jsp, by clicking on "Alfabetiskt på läkemedel" and

13 The provisional standard for the natural female hormone 17 beta oestradiol is also new. This subject however is beyond the range of this report.

then on the substance or ATC code concerned. Environmental information is available for 2064 pharmaceutical products, but the number of active substances in these products is not easy to discover.

SWISS PROVISIONAL STANDARDS

Since 2006 in Switzerland, the large-scale "MicroPoll Strategy" project has been underway with the objective of reducing micropollutants in wastewater and surface water (www. bafu.ch). The project has derived provisional standards for various emerging substances, including 13 pharmaceuticals: namely, atenolol, azithromycin, bezafibrate, carbamazepine, clarothromycin, diclofenac, erythromycin, ibuprofen, mefenamic acid, metoprolol, naproxen, sulfamethoxazole and trimethoprim. (http://www.oekotoxzentrum.ch/expertenservice/ qualitaetskriterien/vorschlaege/index). The procedure also included a number of other substances for which it was concluded that, at this time, no standards can be derived: namely, the iodinated X-ray contrast media diatrizoate, iomeprol and iopamidol, iopromide, the beta-blocker sotalol and 10,11−dihydro10,11dihydroxycarbamazepine, a carbamazepine metabolite.

The derivation is in accordance with the method that is used for WFD priority substances; it has an ecotoxicological base and safety factors are applied. Secondary poisoning risks are not addressed.

The maximum allowable concentration values (MACEQS) range between 0.09 ug/L for azithromycin and 1100 μg/L for trimethoprim, both antibiotics. The annual average values (A AEQS) range between 0.04 ug/L for the antibiotic erythromycin and150 μg/L for the beta-blocker atenolol.

PHARMACEUTICALS: GERMAN STANDARDS IN PREPARATION

In North Rhine-Westphalia (Germany), work has been done in the past on guide-values for pharmaceuticals in surface water. These guide-values can be found in the manual for monitoring surface water in North Rhine-Westphalia: Leitfaden Monitoring Oberflächengewässer Teil D / Anlage 4 Stoffe: Umweltqualitätsnormen und Orientierungswerte (http://wiki.flussgebiete.nrw.de/img_ auth.php/f/f8/D4_Version1_Aug09_neu.pdf). Apparently, these guide-values have not (yet) been given official status.

Guide-values have been established for a total of 23 pharmaceuticals: various painkillers, cardiovascular agents, the antiepileptic carbamazepine and the iodinated X-ray contrast medium iopamidol. The guide-values have different backgrounds (for the details, see the standard list):

- For most of the substances the guide-value is a preventive precautionary value established at 0.1 ug/L.
- For six substances the guide-value is based on standards for substances that are specific to a river-basin area [Länderarbeitsgemeinschaft Wasser (LAWAO 10.03 II): Entwicklung von Qualitätsnormen zum Schutz aquatischer Biota in Oberflachengewässern für flussgebietsspezifische Stoffe (II)].
- For two substances the guide-value is based on a Predicted No Effect Concentration (PNEC) derived within a large research project of the Bund/Länderausschuss für
- Chemikaliensicherheit (BLAC) into pharmaceuticals in 2003 [http://www.blac.de/servlet/is/2146/P2c.pdf]. For these two substances (carbamazepine and propanolol) the standard is therefore based on ecotoxicological data. For carbamazepine, chronic toxicity data were

used with a safety factor of 10, for propanolol the standards is based on acute data with a safety factor of 1,000.

- For diclofenac, despite the much higher PNEC value, a preventive value of 0.1 ug/L is established because of the very high sensitivity of avifauna (birds) to this pharmaceutical.
- For clofibrate acid, a preventive value of 10 ug/L is established.

ANNEX 7

TARGET VALUES IN DRINKING WATER AND DRINKING WATER SOURCES

Q21 TARGET VALUES FOR DRINKING WATER

The drinking water sector has formulated new target values within the BTO "Q21 Water quality for the 21st century" project. These consist of ethical limits that are to be striven after and go beyond what is legally required. The central notion is that environmentally-alien substances do not belong in drinking water, but that their presence cannot be completely prevented. For this reason drinking water companies, in any event, apply the standstill principle: concentrations and toxic activities may not increase. Moreover, target values are developed for maximum concentrations of environmentally-alien substances, derived from safe limit values for food additives and based on the assumption that a maximum of 10% of the toxic load may come from consuming drinking water. According to these target values, drinking water may contain a maximum of 10 ng/L of a genotoxic substance or a steroid hormone, such as female hormones (oestrogens) or glucocorticosteroids, and 0.1 ug/L of most other substances, such as pharmaceuticals. The concentration of all genotoxic substances and steroid hormones combined may not exceed 50 ng/L; for other substances, the maximum total load is 1 ug/L. The target values mostly coincide with the current standards, but they are clearly stricter in the case of genotoxic substances.

Target values are voluntary ethical limits that are to be worked toward and go beyond what is in the law. Frequently they are, as yet, not attainable. They offer water companies a guide for their research, water treatment design and lobbying of government entities and parties in the water cycle, and provide them with a point of reference upon the discovery of a new substance. If the concentration is below the target value, then there is no cause for concern; if it is above the target value, then further research and actions are advisable. (Source: http://www.kwrwater.nl/page.asp?id=1806).

ANNEX 8

CALCULATING LIMIT VALUES IN DRINKING WATER AND DRINKING WATER SOURCES

The fundamental principle of a health limit value for drinking water is a safe daily intake (Versteegh et al., 2003; Versteegh et al., 2007; Schriks et al., 2010). This intake is known as a Tolerable Daily Intake (TDI) or an Acceptable Daily Intake (ADI).

For the calculation of a TDI or ADI, the assumptions used are a body weight of 60 or 70 kg and a drinking water consumption of 2 litres per day. Moreover, an allocation factor of exposure via drinking water of 10 % is applied. This approach ensures that the total daily intake from all possible sources – other than drinking water – does not exceed the TDI.

From this, one can deduce that:
The health limit value for drinking water = (TDI x bw x P)/C

Where:
TDI = tolerable daily intake
Bw = bodyweight, usually 60 or 70 kg;
P = contribution of drinking water to total exposure
C = drinking water consumption, usually 2 litres per day.

Such a value is however not always available for pharmaceuticals. As an alternative a Maximum Residue Limit (MRL) is used (Versteegh et al., 2003; Versteegh et al., 2007), which can then be converted into an ADI or TDI. If an MRL is also not available, then a minimum therapeutically effective dose can be used with a safety factor of 100 (Versteegh et al., 2003; Versteegh et al., 2007; WHO, 2011). Also, for pharmaceutical metabolites or transformation products, use can sometimes be made of a provisional TDI or ADI derived on the basis of toxicological literature data from laboratory animals. In such cases, a safety factor of 100 is applied. This is made up of a factor of 10 for variations between laboratory animals and humans, and a factor of 10 to correct for variations of sensitivity within a single species.

An example of a pharmaceutical for which the minimum therapeutically effective dose has been used to derive a health limit value is phenazone (Versteegh et al., 2003; Versteegh et al., 2007). The minimum therapeutically effective dose is 250 mg/day. From this a provisional ADI of 250/100 = 2.5 mg per person per day can be derived. The provisional health limit value is therefore 2.5 * 10% / 2 L water per person = 125 µg/L .

On the basis of the above methods, RIVM has derived toxicological limit values for 29 pharmaceuticals, including X-ray contrast media (Versteegh et al., 2003; Versteegh et al., 2007; van der Aa et al., 2011a). The values range between 1 µg/L for the beta-blocker bisoprolol and 415 mg/L for the iodinated X-ray contrast medium iopamidol. In addition, KWR has also derived provisional limit values for 13 other pharmaceuticals and their transformation

products (Schriks et al., 2010; De Jongh et al., 2012). In its report, the WHO presents an overview of international publications in which this pharmaceutical risk assessment method for drinking water is applied.

ANNEX 9

PREFERRED TECHNIQUES FOR THE REMOVAL OF PHARMACEUTICALS AT WWTPS (GRONTMIJ 2011)

Preferred techniques	Removal efficiency	Energy use	Waste stream
Activated carbon filtration	70%	Low	Present
Ozonisation combined with supplementary activated carbon filtration	90%	Average	None
Advanced oxidation process (AOP) combined with supplementary activated carbon filtration	90%	Average	None
Nanofiltration combined with supplementary activated carbon filtration	95%	High	Present