UvA-DARE (Digital Academic Repository)

Assessing the discharge of pharmaceuticals to the Dutch coastal zone

Walraven, N.; Laane, R.W.P.M.

DOI

[10.1007/978-0-387-09808-1_1](https://doi.org/10.1007/978-0-387-09808-1_1)

Publication date

2009

Document Version

Submitted manuscript

Published in

Reviews of Environmental Contamination and Toxicology

[Link to publication](#)

Citation for published version (APA):

Walraven, N., & Laane, R. W. P. M. (2009). Assessing the discharge of pharmaceuticals to the Dutch coastal zone. *Reviews of Environmental Contamination and Toxicology*, 199, 1-18. https://doi.org/10.1007/978-0-387-09808-1_1

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Assessing the discharge of pharmaceuticals to the Dutch coastal zone of the North Sea

N. Walraven¹ and R.W.P.M. Laane²

¹ GEOCONNECT

Meester Dekkerstraat 4 I

1901 PV Castricum

² National Institute for Coastal and Marine
Management (RIKZ)

P.O.Box 20907

2500 EX The Hague

The Netherlands

Werkdocument RIKZ-ZDW 2006.010X

November 2006

Contents

Abstract	5
1 Introduction	7
2 Background information	9
2.1 Consumption (use) of pharmaceuticals in the Netherlands	9
2.2 Emission route of pharmaceuticals	10
3 Methods	13
3.1 Data inventory	13
3.2 Load Calculations	13
4 Results and Discussion	15
4.1 Occurrence of pharmaceuticals in surface-, sewage- and industrial water in the Netherlands	15
4.2 Pharmaceutical loads	20
4.3 Mass balance of pharmaceutical loads	22
4.4 Discharge of hazardous substances to the DCZ: pharmaceuticals vs OSPAR priority substances	22
4.5 Environmental impact of discharged pharmaceuticals	23
5 Conclusions	27
References	29
Appendices	33

Abstract

The annual median discharge of over 100 pharmaceuticals to the Dutch coastal zone (DCZ) is assessed. Calculations are based on pharmaceutical concentrations in surface-, sewage- and industrial water in the Netherlands.

In 2002, riverine discharge to the DCZ for individual pharmaceuticals varied from 0 (concentration below limit of detection) to 27 ton/year. The discharge of 75% percent of all analysed pharmaceuticals was lower than 2 ton/ in 2002. Highest loads were calculated for the X-ray contrast media, e.g. values in the range of 18 to 27 ton/year for iopromide.

The top 20 pharmaceuticals discharged by rivers to the DCZ is dominated by the X-ray contrast media (n=7), followed by antibiotics (n=6), analgesics/antipyretics/anti-inflammatory drugs (n=2), beta blockers (n=2), fibrates/lipid regulators (n=1), veterinary antibiotics (n=1) and others (n=1). The direct discharge (sewage water and industrial water) of pharmaceuticals to the DCZ in 2002 for individual pharmaceuticals varied from 0 to 0.27 ton/year for sewage water and from 0 to 0.33 ton/year for industrial wastewater. Highest loads were calculated for sotalol (beta blocker) and diatrizoic acid (X-ray contrast medium) in sewage water and industrial wastewater respectively. The discharge of pharmaceuticals to the DCZ due to direct discharge is <5% compared to riverine discharge.

The discharge of these pharmaceuticals to the DCZ in 2002 is in the same order of magnitude as the discharge of the mandatory OSPAR substances cadmium (8.8-10 ton/year) and mercury (3.3 ton/year) in 2002 and higher than the discharge of the mandatory substance lindane (0.041 to 0.055 ton/year) and the recommended substance PCBs (0.217 ton/year). Here it must be taken into account that pharmaceuticals are biological active compounds designed to be active at relatively low concentrations.

Although some pharmaceuticals are discharged in significant amounts to the DCZ, the human and ecotoxicological risks are largely unknown. To determine the environmental hazard and risk of discharged pharmaceuticals to the marine environment, future research should focus on a base line study and a risk assessment of the discharged pharmaceuticals in the Dutch coastal zone.

1 Introduction

The aspect of pharmaceutical chemicals in the environment was occasionally mentioned in the late 1970s by Highnite and Azarnoff (1977) and mid-80s by Richardson and Bowron (1985) and Rogers *et al.* (1986). Little attention has been paid to these substances as potential environmental pollutants until the early 1990s (Weigel, 2003). Stan and Linkerhägner (1992) were among the first to identify high concentrations of clofibric acid, metabolite of the lipid regulating agents of the pharmaceuticals clofibrate and etofibrate, in groundwater. Several research groups followed and revealed the presence of a vast array of pharmaceutical residues in municipal wastewater, surface water, groundwater and drinking water in concentrations varying from ng/l to µg/l (a.o. Stan *et al.* 1994; Hirsch *et al.*, 1996; Stan and Heberer, 1996; Stumpf *et al.*, 1996; Buser *et al.*, 1998^{a,b}; Hartmann *et al.*, 1998; Ternes, 1998; Buser *et al.*, 1999; Hartig *et al.*, 1999; Hirsch *et al.*, 1999; Ternes and Hirsch, 2000; Heberer, 2002; Tixier *et al.*, 2003; Weigel *et al.*, 2004; Comoretto and Chiron, 2005).

To identify the presence of human and veterinary pharmaceuticals in Dutch surface -, drinking -, sewage - and industrial water, an extensive monitoring campaign was conducted between 2000 and 2003 (a.o. Schrap *et al.*, 2003; Versteegh *et al.*, 2003; Mons *et al.*, 2000, 2003; Sacher and Stoks, 2003). During these campaigns around 100 active ingredients were selected from a total of around 850 different human pharmaceuticals and 200 veterinary pharmaceuticals used in the Netherlands. These active ingredients were selected on basis of available analytical techniques to identify and quantify them, concentrations reported in other studies and the estimated risk to the aquatic environment (Schrap *et al.*, 2003). Monitoring focussed mainly on the active ingredients and no effort was made to detect their metabolites. The selected categories of pharmaceuticals included antibiotics, coccidiostatics, analgesics, x-ray contrast media, drugs used to treat coronary vascular disease, antineoplastic drugs and antiepileptics.

Sewage water from a residential area contained household analgesics, lipid-lowering agents, beta-blockers and antiepileptics in concentrations up to tens of µg/l (Schrap *et al.*, 2003). They found that concentrations of pharmaceuticals in general municipal sewage water and in influent water at sewage treatment plants (STPs) are very similar to sewage water from the residential areas, although containing higher concentrations of specific antibiotics and x-ray contrast media. In general concentrations of pharmaceuticals in Dutch surface water are significantly lower than in sewage water, ranging from a few

to several hundreds of ng/l (Schrap *et al.*, 2003). Substances most frequently identified during the campaigns described above in Dutch surface water (in at least 50% of the locations) were almost all x-ray contrast media, four analgesics (acetylsalicylic acid, diclofenac, ibuprofen and naproxen), two antiepileptics (carbamazepine and primidone), two beta-blockers (sotalol and atenolol), two antibiotics (azitromycin and sulfamethoxazole) and one anaesthetic (lidocaine) (Schrap *et al.*, 2003). Pharmaceuticals were only detected incidentally in Dutch ground and drinking water (Mons *et al.*, 2003; Versteegh *et al.*, 2002; Mons *et al.*, 2003).

Some pharmaceuticals present in Dutch sewage and surface water will finally end up in the North Sea. Unfortunately no measurements of concentrations of pharmaceuticals in seawater of the Dutch coastal zone of the North Sea were performed. However, in studies by others, clofibric acid (Buser *et al.*, 1998^a; Weigel, 2003) and caffeine (Weigel, 2003) were detected at ng/l level in the North Sea (German Bight, English Coast and Norwegian Coast). Diclofenac, ibuprofen, propyphenazone and ketoprofen were also measured but could not be detected or identified unambiguously in the North Sea (German Bight, English Coast and Norwegian Coast) (Weigel, 2003). In summary, the number of pharmaceuticals studied in the the North Sea is limited (n=6) and it is therefore expected that more pharmaceuticals beside clofibric acid are present in seawater of the North Sea (German Bight, English Coast and Norwegian Coast).

Since pharmaceuticals are biologically active compounds that are designed to instigate pharmacological effects at relatively low concentrations, it is feasible that pharmaceuticals may also affect non-target organisms in the aquatic environment (Rijs *et al.*, 2003). If the emissions sources and fluxes of pharmaceuticals to the DCZ are known and quantified it will be possible to determine measures for specific (groups of) pharmaceuticals to prevent further contamination.

The input of both human and veterinary pharmaceuticals to the Dutch coastal zone (DCZ) is assessed in this study. All public data on pharmaceuticals in the Dutch aquatic environment that can end up in the water of the DCZ is collected and emissions calculations are performed to determine the riverine input and direct discharge of circa 100 active agents of pharmaceuticals to the North Sea.

The sources, presence and impact of pseudo hormones and hormones in Dutch aquatic environment are published elsewhere (Belfroid *et al.*, 1999; Vethaak *et al.*, 2002).

2 Background information

2.1 Consumption (use) of pharmaceuticals in the Netherlands

The company Farminform collects figures on the yearly sales of pharmaceuticals in the Netherlands. These figures are however, only available for the pharmaceutical industry. In 1999, Farminform made an exception and made the sales of about 20 pharmaceuticals public (Derksen *et al.*, 2001)(Table 1). Table 1 shows that analgesics are by far the most used pharmaceuticals in 1999 for which sales figures are available.

Table 1 Sales of pharmaceuticals for human application to hospitals, pharmacies and drugstores in the Netherlands in 1999 for 20 active substances expresses as tons/year (source: Derksen *et al.*, 2001).^{Ad 1} The pharmaceuticals are also for veterinary purposes.

Active substance Pharmaceuticals	Sales (tons/year)	Total per substance group (tons/year)
Blood lipid regulators and β blockers		16.3
Bezafibrate	0.3	
Clofibrate	0.2	
Gemfibrozil	5.7	
Metoprolol	10.1	
Anti-epileptics		21.3
Carbamazepine	10.8	
Valproine acid	10.5	
Analgesics		322
Acetylsalicylic acid	28.0	
Paracetamol	223.0	
Naproxen	17.6	
Ibuprofen	48.0	
Diclofenac	5.6	
Oncolytics		<0.2
Cyclophosphamide	0.01	
Bleomycine	<0.1	
Cisplatin	0	
Antibiotics		26.9
Doxycylin1	0.9	
Erythromycin1	1.5	
Amoxicillin1	18.0	
Ciprofloxacin	1.6	
Nitrofurantoin	0.7	
Cefalexin	0.1	
Sulfamethoxazole11	4.1	
Total		382

2.2 Emission routes of pharmaceuticals

There are several routes by which human and veterinary pharmaceuticals can enter the environment. The three most important routes are (Mons *et al.*, 2000) (Figure 1):

1. Direct disposal at manufacturing
2. Excretion with urine and faeces (sewage water) and
3. Dispersion of manure on farming land and runoff.

Figure 1 The fate of pharmaceuticals in water (source: adjusted after Mons *et al.*, 2000).

Human pharmaceuticals are mostly discharged by wastewater from households, hospitals and nursing homes after use via urine and faeces (Mons *et al.*, 2000; Derksen *et al.*, 2001). This wastewater enters the sewerage system and is treated in a STP. From a quantitative point of view, excretion of pharmaceuticals with urine and faeces is much more important than direct disposal at manufacturing (Derksen *et al.*, 2001). Only a small percentage (1-5%) of pharmaceuticals ends up in the wastewater during manufacturing (Mons *et al.*, 2000). Disposal in Dutch households is also quite small. In the Netherlands, 8.3% of all prescribed medicines are not consumed (Blom *et al.*, 1995). Only 3% of non-consumed medicines end up via consumers in the sewer (Blom *et al.*, 1995). The majority of the unused medicines are, however, collected separately after they are handed in to pharmacies. One third (33%) of liquid medicines handed in to pharmacies still ends up in the sewer (Blom *et al.*, 1995).

The fate of veterinary drugs after urinal or faecal excretion differs considerably from the fate of human drugs after excretion (Mons *et al.*, 2000). In general municipal sewage and, therefore, human pharmaceuticals have to pass through a STP prior to entering rivers, streams or coastal zone. Veterinary drugs are more likely to contaminate soil and ground water (without previous waste water treatment) when liquid manure is applied to the soil as fertilizer. It is assumed that veterinary pharmaceuticals will only end up partly in surface waters due to surface run-off (Mons *et al.*, 2000).

Other possible sources of pharmaceuticals to the coastal and marine environment, which are not depicted in Figure 1, are atmospheric deposition and sea-shipping emissions.

The emission of pharmaceuticals to the atmosphere is only mentioned in one study (Hamscher *et al.*, 2002). The exact extent (size) of this source is unknown, but Boxall *et al.* (2003) estimated this source of minor importance compared to other input sources of pharmaceuticals to the environment. Atmospheric deposition as input source of pharmaceuticals to the DCZ is therefore not taken into consideration in this study.

Although some pharmaceuticals (e.g. the antibiotic tetracycline) are mentioned as possible antifouling paint additives (Peterson *et al.*, 1993), Klijnsta (2005) found no commercial available antifouling products, containing pharmaceuticals based on a literature review and internet search. Sea-shipping emissions as input source of pharmaceuticals to water of the DCZ are therefore not taken into consideration in this study.

Acknowledgement

G. van de Haar (KIWA) and H. Dik (RIVM) are acknowledge for delivering the data. M. Schrap (RIZA) deliverde date and she is also acknowledged for the critical comment on the manuscript.

3 Methods

3.1 Data inventory

This inventory on existing data regarding pharmaceutical concentrations in surface -, sewage -, industrial - and marine water in the Netherlands, is based on scientific publications and on information, mainly 'grey' literature and unpublished data, from research institutes (e.g. TNO, RIZA, RIWA, WLB-A, RIVM and STOWA) and universities (e.g. University of Utrecht). In addition to direct contacts with these institutes and universities, a literature search was performed on the Internet and in the databases of university libraries. Appendix A lists the libraries, databases and websites, which were consulted. In addition the keywords used for the search are shown.

3.2 Load Calculations

The load of a specific pharmaceutical and/or metabolite transported by rivers, sewage effluent or industrial effluent to the Netherlands (from neighbouring countries) and to the DCZ is calculated according to the following equations:

Equation 1

$$L-sw_{in} = (Qa_{EYS} \times C_{EYS} + Qa_{LOB} \times C_{LOB} + Qa_{SOD}) \times f_{in} / 10^{12}$$

Equation 2

$$L-sw_{in} = (Qa_{AND} \times C_{AND} + Qa_{MAA} \times C_{MAA} + Qa_{HAR} \times C_{HAR}) \times f_{out} / 10^{12}$$

Equation 3

$$L-sew_{out} = Qa_{SEW} \times C_{SEW} / 10^{12}$$

Equation 4

$$L-ind_{out} = Qa_{IND} \times C_{IND} / 10^{12}$$

Where;

$L-sw_{in}$ = Load of pharmaceuticals entering the Netherlands with surface water in 2002 (ton/year).

$L-sw_{out}$ = Load of pharmaceuticals entering the DCZ with surface water in 2002 (ton/year).

$L-sew_{out}$ = Load of pharmaceuticals entering the DCZ with sewage water in 2002 (ton/year)

$L-ind_{out}$ = Load of pharmaceuticals entering the DCZ with industrial water in 2002 (ton/year).

Qa = Average flow rate at sample location in 2002 ($10^9 \text{ m}^3/\text{year}$).

C = Average concentration of a pharmaceutical in surface water, sewage water (SEW) or industrial water (IND) in 2002 (ng/l).

f = correction factor (not all surface water entering the Netherlands and DCZ were sampled, with f this load is estimated). (EYS=Eijsden; LOB=Lobith; SOD=Schaar van Ouden Doel; AND=Andijk-Ysselmeer; MAA=Maassluis; HAR=Haringvliet).

In this study the minimum, maximum, median and average loads of individual pharmaceuticals are calculated in the sampling year 2002. Values below the limit of detection are replaced with zero to get a conservative estimate of pharmaceutical loads (method 1). Values below the limit of detection are also replaced with the detection limit itself to get a maximum value of pharmaceutical loads (method 2). The average flow rate (Q_a) at the sampling locations EYS, LOB and SOD is obtained from the database 'Waterbase' (www.waterbase.nl) which contains flow rate data based on daily averages. The average flow rate (Q_a) at the sampling locations AND, MAA and HAR, and for sewage water and industrial water entering the DCZ is obtained from the OSPAR year report (2002) of the Netherlands. All values are listed in table 2.

Table 2. Average flow rates of surface water at Eysden (EYS), Lobith (LOB), Schaar van Oude Doel (SOD), Andijk (AND), Maassluis (MAA), Haringvliet (HAR) and others, and sewage water and industrial water entering the DCZ in the Netherlands in 2002 (see Fig.2).

Sample location	Qa (10 ⁹ m ³ /year)	Source
<i>Surface water entering the Netherlands (inflow)</i>		
EYS	10.925	www.waterbase.nl
LOB	93.793	www.waterbase.nl
SOD (others)	2.735	www.waterbase.nl
Others (excluding SOD) ¹	0.504	Netherlands Hydrological Society (2004)
TOTAL-in	107.860	
<i>Surface water entering the DCZ (outflow)</i>		
AND	19.856	OSPAR (2002)
MAA	50.188	OSPAR (2002)
HAR	30.332	OSPAR (2002)
Others	9.795	OSPAR (2002)
TOTAL-out	110.171	
<i>Sewage water entering the DCZ (outflow)</i>		
TOTAL-out	0.168	OSPAR (2002)
<i>Industrial water entering the DCZ (outflow)</i>		
TOTAL-out	0.002	OSPAR (2002)

¹ 3% of total (according to Netherlands Hydrological Society, 2004)

Based on the figures in table 2, the f values for all pharmaceuticals are calculated according to the following equations:

Equation 5

$$f_{in} = \frac{Qa_{TOTAL-in}}{Qa_{EYS} + Qa_{LOB} + Qa_{SOD}}$$

Equation 6

$$f_{out} = \frac{Qa_{TOTAL-out}}{Qa_{AND} + Qa_{MAA} + Qa_{HAR}}$$

Where;

f_{in} = correction factor to calculate the load of pharmaceuticals entering the Netherlands with surface water in 2002.

f_{out} = correction factor to calculate the load of pharmaceuticals entering the DCZ with surface water in 2002.

Qa = Average flow rate at sample location in 2002 (10⁹ m³/year). Data are obtained from table 2.

$TOTAL-in$ = EYS+LOB+SOD+others

$TOTAL-out$ = AND+MAA+HAR+others;

4 Results and Discussion

The constructed database comprises over 100 pharmaceuticals, both human and veterinary, which have been measured in surface, sewage and industrial water from the Netherlands in the period between 1996 and 2005. Most analyses have been performed on surface water samples (n=634) and only a limited number on samples of sewage water (n=13) and industrial water (n=10) have been analysed. It should also be noticed that the measurements on industrial waters are highly biased since mainly effluent water from industries that discharge large quantities of pharmaceuticals (e.g. pharmaceutical companies and hospitals) has been sampled.

4.1 Occurrence of pharmaceuticals in surface-, sewage- and industrial water in the Netherlands

The concentrations (>LOD) of pharmaceuticals in surface-, sewage- and industrial water from the Netherlands are visualized in box-whisker plots in figure 2 to 4 respectively. In these figures, 7 pharmaceutical groups are distinguished, 1) antibiotics, 2) veterinary antibiotics, 3) analgesics / antipyretics / anti-inflammatory drugs, 4) x-ray contrast media, 5) fibrates / lipid regulators, 6) beta blockers and 7) others (antihelminthic, bronchitis/asthma, antineoplastics, anti-oestrogen, neuroleptics, anaesthetics, steroids and antifungal veterinary drug).

Surface water

Figure 3 shows that only 58 pharmaceuticals of the total of 102 listed pharmaceuticals in the database have, in one or more surface water samples, concentrations above the LOD. Concentrations of pharmaceuticals in Dutch surface water varied from 0.02 ng/l (oxolinic acid in surface water from Nieuwersluis) to 830 ng/l (diclofenac in surface water from Meuse river at Roosteren). The highest median concentrations in surface water are observed for the X-ray contrast media, with median concentrations ranging from 25 to 145 ng/l. The pharmaceuticals with the highest median concentration of each pharmaceutical group are: oxytetracyclin (49 ng/l), dimetridazol (16 ng/l), diclofenac (40 ng/l), iopromide (145 ng/l), bezafibrate (30 ng/l), sotalol (60 ng/l) and carbamazepine (150 ng/l). The geographical distribution of the median concentrations in ng/l (method 1) of these seven pharmaceuticals in 2002 are visualised in Appendix B. The observed concentrations of pharmaceuticals in the Netherlands are in agreement with the concentrations measured in the river Rhine (Basel, Düsseldorf and Cologne) in 2000 (Weil and Knepper, 2006).

Figure 3 Box-whisker plot of concentrations of pharmaceuticals in surface water in the Netherlands in the period between 1996 and 2005 (• outlier)

The only uniform patterns that can be observed in the figures in Appendix B are the relatively low concentrations of pharmaceuticals in the surface waters in the northern provinces in comparison with the more southern provinces. It is however noted that less surface waters are sampled in the northern provinces than in the southern provinces. In general, the highest concentrations are measured in the main rivers - Rhine (LOB), Meuse (EYS and MAA), Schelde (SOD) and Amsterdam

Rijnkanaal (NGN) – which are situated in the southern provinces in the Netherlands. Iopromide, carbamazepine and sotalol are present (concentrations > limit of detection, LOD) at almost all sampled locations.

Most likely no uniform pattern is observed in the geographical distribution of the mean pharmaceutical concentrations since only a limited number of samples are taken and analysed at each location. In addition, the sampling date of each location varied considerably. If pharmaceutical concentrations strongly depend on the flow rate of the river, possible trends are blurred.

However, a non-significant relation is found between the flow rate and the concentration of carbamazepine, diclofenac, iopromide and bezafibrate in the river Rhine near Lobith for the period 2001-2005 (Appendix C). Correlation coefficients - expressed as R^2 – between flow rate and the concentration of carbamazepine, diclofenac, iopromide and bezafibrate are quite low, varying from 0.06 for bezafibrate to 0.15 for carbamazepine. This points at another variable that influences pharmaceutical concentrations in surface water in time. This variable is most likely the application period and the amount of pharmaceuticals discharged to the environment. Pharmaceuticals are, in contrast to some other chemical substances (e.g. nitrate and phosphate), discharged year round. However, discharge of some pharmaceuticals (e.g. analgesics) will be higher during winter times than summer times. This might explain why no relationship is found between flow rate and diclofenac concentrations in surface waters near Lobith.

Sewage water effluent

Pharmaceutical concentrations in sewage water effluents are in general higher than in surface water.

Figure 4 shows that only 32 pharmaceuticals of the total of 102 listed pharmaceuticals in the database have, in one or more sewage water effluent samples, concentrations above the LOD. Concentrations of pharmaceuticals in Dutch sewage water effluent varied from 11 ng/l (dimetridazol) to 10 µg/l (iomeprol). The highest median concentrations in sewage water effluents are observed for the X-ray contrast media, with median concentrations ranging from 190 to 3100 ng/l. The pharmaceuticals with the highest median concentration of each pharmaceutical group are: anhydro-erythromycin (310 ng/l), dimetridazol (12 ng/l), diclofenac (520 ng/l), iomeprol (3.1 µg/l), gemfibrozil (580 ng/l), sotalol (1.1 µg/l) and carbamazepine (490 ng/l).

Industrial wastewater effluents

Pharmaceutical concentrations in industrial wastewater effluents are in general higher than in surface water and in sewage water effluents. It should be noted that most industrial wastewater samples are from pharmaceutical industries and hospitals.

Figure 4 Box-whisker plot of concentrations of pharmaceuticals in sewage water effluent in the Netherlands in 2002 (• outlier)

Figure 5 shows that only 54 pharmaceuticals of the total of 102 listed pharmaceuticals in the database have, in one or more industrial wastewater effluent samples, concentrations above the LOD. Concentrations of pharmaceuticals in Dutch industrial wastewater effluents varied from 11 ng/l (terbutalin) to 1.1 mg/l (iohexol). The highest median concentrations in sewage water effluents are observed for the X-ray contrast media, with median concentrations ranging from

Figure 5 Box-whisker plot of concentrations of pharmaceuticals in industrial waste water in the Netherlands in 2002 (• outlier)

540 ng/l to 665 µg/l. The pharmaceuticals with the highest median concentration of each pharmaceutical group are: oxytetracycline (68 µg/l), dimetridazole (11.3 µg/l), paracetamol (21.4 µg/l), iomeprol (665 µg/l), gemfibrozil (3.73 µg/l), sotalol (1.7 µg/l) and ifosfamide (995 ng/l).

4.2 Pharmaceutical loads

The loads of pharmaceuticals have been calculated for the year 2002, because concentrations of pharmaceuticals in sewage- and industrial water were measured only in 2002. Most surface water samples were also sampled and analysed in 2002. Two methods have been used to calculate pharmaceutical loads (see Methods): method 1 gives a conservative estimate and with method 2 the maximum pharmaceutical load is calculated. Only the median values (method 1) are described and discussed, unless indicated (stated) otherwise. For all other values see Appendix).

Riverine discharge to the DCZ

Riverine discharge of pharmaceuticals to the DCZ in 2002 varied from 0 (concentration below LOD) to 27 ton/year. Highest loads are calculated for the X-ray contrast media, with values in the range of 18 to 27 ton/year for iopromide. For many pharmaceuticals loads couldn't be calculated because all concentration measurements were below the detection limit. However, by replacing the detection limit with the value of the detection limit, the maximum load for these pharmaceuticals was calculated (method 2). The load of pharmaceuticals with concentrations below the detection limits vary approximately between 0 and 1 ton/year.

The riverine discharge of 75% of the studied pharmaceuticals is less than 2 ton/year (based on method 2). These pharmaceuticals will not be described in detail. In this study is focussed on the 20 pharmaceuticals with the highest riverine discharge to the DCZ. The median input loads of the top 20 pharmaceuticals discharged to the DCZ by rivers are listed in table 3.

The top 20 pharmaceuticals discharged to the DCZ is dominated by the X-ray contrast media (n=7), followed by antibiotics (n=6), analgesics/antipyretics/anti-inflammatory drugs (n=2), beta blockers (n=2), fibrates/lipid regulators (n=1), veterinary antibiotics (n=1) and others (n=1).

Direct discharge to the DCZ (sewage water and industrial water effluents)

Although the concentrations of many pharmaceuticals in sewage water effluents and industrial water effluents are higher than in surface water, the estimated loads of pharmaceuticals due to direct discharge to the DCZ is low compared to the riverine input to the DCZ. This is due to the huge difference in flow rate between surface waters and sewage water/ industrial water entering the DCZ (see table 2).

The direct discharge loads of the top 20 pharmaceuticals are shown in table 3. The highest pharmaceutical load in sewage water effluent and industrial water water to the DCZ is calculated for sotalol, ranging from 0.16 to 0.27 ton/year with a median of 0.18 ton/year, and diatrizoic

Pharmaceutical	Riverine discharge	Direct discharge		Total discharge	Riverine input	Input-total discharge	Sales (1999)
	(Ton/year)	SWTP	Industrial		(Ton/year)	(Ton/year)	(Ton)
Iopromide	22.611	0.000	0.000	22.611	42.726	20.115	
Carbamazepine	12.064	0.082	0.001	12.147	7.467	-4.680	10.8
Diatrizoic acid	8.989	0.047	0.067	9.103	15.261	6.158	
Iopamidol	8.841	0.000	0.000	8.841	15.608	6.767	
Iomeprol	6.418	0.032	0.001	6.451	7.442	0.992	
Sulfamethoxazol	5.245	0.016	0.000	5.261	2.745	-2.516	4.1
Iohexol	4.637	0.020	0.001	4.658	6.775	2.117	
Sotalol	4.631	0.185	0.003	4.819	9.050	4.231	
Diclofenac	3.984	0.087	0.003	4.075	10.545	6.470	
Metoprolol	2.808	0.081	0.001	2.890	2.530	-0.360	
Anhydro-erythromycin	2.534	0.052	0.001	2.587	2.205	-0.382	
Ibuprofen	2.341	0.049	0.009	2.399	1.344	-1.055	48.0
Azitromycin	2.093	0.034	0.000	2.128	2.200	0.073	
Dimetridazol	2.066	0.001	0.000	2.067	0.835	-1.232	
Iothalamic acid	1.845	0.030	0.006	1.882	3.312	1.430	
Lincomycin	1.322	0.000	0.000	1.322	0.053	-1.269	
Bezafibrate	1.262	0.000	0.000	1.263	0.920	-0.343	0.3
Clarithromycin	1.212	0.042	0.000	1.254	1.199	-0.055	
Roxitromycin	1.102	0.000	0.000	1.102	1.276	0.174	
Ioxithalamic acid	0.895	0.032	0.013	0.940	2.785	1.845	

Table 3 Annual median loads of top 20 pharmaceuticals discharged to the DCZ, riverine input to the Netherlands and difference between discharge and input in 2002 and the sales in 1999.

acid, ranging from 0 to 0.327 ton/year with a median of 0.067 ton/year respectively. The discharge of pharmaceuticals to the DCZ is < 5% compared to riverine discharge of pharmaceuticals to the DCZ.

Riverine input to the Netherlands

Loads of pharmaceuticals that entered the Netherlands with surface water from neighbouring countries in 2002 are in the order of 0 to 70 ton/year (Appendix D). Highest loads are calculated for the X-ray contrast media, with values in the range of 15 to 70 ton/year for iopromide. Barreveld *et al.* (2001) estimated the load of carbamazepine entering the Netherlands near Lobith in 1997 at (to be) an median of 4.1 ton/year and an average of 6.3 ton/year. These values agree well with the loads calculated in 2002 for carbamazepine (total of 7.5 ton/year) in this study. The median loads of the top 20 pharmaceuticals entering the Netherlands by rivers Rhine, Meuse and Scheldt are listed in table 3. The median loads vary from 0.05 ton/year for lincomycin to 47.7 ton/year for iopromide.

For many pharmaceuticals loads couldn't be calculated because all concentration measurements were below the detection limit. However, by replacing the detection limit with the value of the detection limit, the maximum load for these pharmaceuticals was calculated (method 2). The load of pharmaceuticals with concentrations below the detection limits vary approximately between 0 and 1 ton/year.

4.3 Mass balance of pharmaceutical loads

The difference between the load of pharmaceuticals entering the Netherlands by rivers and leaving the Netherlands by rivers and direct discharge is a measure for the amount of pharmaceuticals added to or removed from surface water in the Netherlands (table 3).

It is remarkable that the amount of all top 20 X-ray contrast media entering the Netherlands is higher than leaving the Netherlands. Amounts of x-ray contrast media removed from surface water in the Netherlands vary (at least) from 1 ton/year for iomeprol to 20 ton /year for iopromide. These amounts are most likely not removed from the surface water by sewage water treatment plants (STPs). Schrap *et al.* (2003) determined that removal rates for x-ray contrast media by STPs in the Netherlands is smaller than 10%. Ternes and Hirsch (2000) found that X-ray contrast media were not removed at all in STPs in Germany. How X-ray contrasts are removed from surface water is yet unknown. Possible they adsorb to the suspended matter end up in the river sediment.

The amount of sotalol, diclofenac, azitromycin and roxitromycin entering the Netherlands is also higher than the amount leaving the Netherlands. However, the pharmaceuticals are in contrast to the X-ray contrast media removed (slightly) more efficient from surface water in STPs. Schrap *et al.* (2003) report removal efficiencies of 8-12 %, 48-67 % and 6-63 % for sotalol, diclofenac and azitromycin respectively. No data on removal rates of roxitromycin, during sewage water treatment, are found in literature.

All other pharmaceuticals listed in Table 3 show a net addition of pharmaceuticals in the Netherlands. The amount of bezafibrate sold in the Netherlands in 1999 (Derksen *et al.*, 2001) is in good agreement with the net addition of bezafibrate in 2002 (table 3).

Table 1 shows that analgesics are by far the most used (read: sold) pharmaceuticals in 1999. However, the only analgesics in the top 20 (Table 3) are diclofenac and ibuprofen. Paracetamol doesn't occur in the top 20, although 223 tons is sold in the Netherlands in 1999. The low discharge of paracetamol to the DCZ (0.32 ton/year in 2002) is caused by the high removal efficiency of paracetamol in Dutch STPs. Schrap *et al.* (2003) measured removal percentages of 100 % for paracetamol. Fent *et al.* (2005) also report removal percentages of paracetamol of 100 %. Although less ibuprofen and diclofenac are sold compared to paracetamol (Table 1), more of these pharmaceuticals are discharged to the DCZ due to the lower removal percentage of these pharmaceuticals (52-96 % and 48-67 % for ibuprofen and diclofenac respectively) in Dutch STPs (Schrap *et al.*, 2003).

4.4 Discharge of hazardous substances to the DCZ: pharmaceuticals vs OSPAR priority substances

The following substances were monitored on a mandatory basis in 2002 in the framework of the OSPAR convention for the protection

.....
Table 4 Ranking of the discharge of mandatory and recommended OSPAR substances and pharmaceuticals to the DCZ in 2002.

of the marine environment of the North Sea: total Hg, total Cd, total Cu, total Zn, total Pb, lindane, ammonia expressed as N, nitrates expressed as N, orthophosphates expressed as P, total N and total P. PCBs were measured on a voluntary basis. The discharge of these substances to the DCZ in 2002 is listed in Table 4. The discharge of 10 pharmaceuticals to the DCZ in 2002, as estimated in this study is, for comparison purposes, also presented in Table 4.

Ranking	Substance	Sum riverine and direct input to DCZ (ton)	Year	Reference
1	Total-N	429,000	2002	OSPAR (2004)
2	NO ₃ ⁻ -N	309,000	2002	OSPAR (2004)
4	NH ₄ ⁺ -N	16,000	2002	OSPAR (2004)
3	Total P	29,000	2002	OSPAR (2004)
5	PO ₄ ³⁻ -P	10,000	2002	OSPAR (2004)
6	Zn	2,159	2002	OSPAR (2004)
7	Cu	528	2002	OSPAR (2004)
8	Pb	386	2002	OSPAR (2004)
9	Iopromide	22.6	2002	This study (median value)
10	Carbamazepine	12.1	2002	This study (median value)
11	Cd	8.8-10	2002	OSPAR (2004)
12	Diatrizoic acid	9.1	2002	This study (median value)
13	Iopamidol	8.8	2002	This study (median value)
14	Iomeprol	6.4	2002	This study (median value)
15	Sulfamethoxazol	5.3	2002	This study (median value)
16	Sotalol	4.8	2002	This study (median value)
17	Iohexol	4.7	2002	This study (median value)
18	Diclofenac	4.1	2002	This study (median value)
19	Hg	3.3	2002	OSPAR (2004)
20	Metoprolol	2.9	2002	This study (median value)
21	PCBs (1)	0.217	2002	OSPAR (2004)
22	γ-HCH (lindane)	0.041-0.055	2002	OSPAR (2004)

(1) IUPAC Nos 28, 52, 101, 118, 153, 138, 180

Table 4 shows that the discharge of the pharmaceuticals iopromide, carbamazepine, diatrizoic acid, iopamidol, iomeprol, syulfamethoxazol, sotalol, iohexol, diclofenac and metoprolol to the DCZ is in the same order of magnitude as the discharge of the mandatory OSPAR substances cadmium and mercury. The discharge of the listed pharmaceuticals is an order of magnitude larger than the discharge of the recommended OSPAR substance PCBs and two orders than the mandatory substance lindane.

4.5 Environmental impact of discharged pharmaceuticals

Although some pharmaceuticals are discharged in significant amounts to the DCZ, the human and ecotoxicological risks are largely unknown (Jørgenson and Halling-Sørensen, 2000; Sanderson *et al.*, 2004). According to Sanderson *et al.* (2004) ecotoxicological data are

available for less than 1% of human pharmaceuticals in the open-peer reviewed literature and ecotoxicological databases (ECETOX (EU) and ECOTOX (US)).

Sanderson *et al.* (2004) developed a quantitative prioritization tool for ranking and prioritization of environmental risk assessment of pharmaceuticals based on: 1) their ranked predicted aquatic toxicity, 2) removal in sewage treatment plants, 3) potential to bioaccumulate and 4) how many compound each class comprises, which was used as a assumed surrogate for volumes as classes with large diversity typically will have increased volumes relative to classes with low diversity. According to this tool modifying additives to pharmaceuticals (e.g. paraffin, anionic and nonionic surfactants) were the most toxic classes. However, these substances are not the active ingredients of pharmaceuticals. Cardiovascular, gastrointestinal, antiviral, anxiolytic sedatives hypnotics and antipsychotics, corticosteroid, and thyroid pharmaceuticals were the predicted most hazardous therapeutic classes. Predicted information on individual compounds within the different classes, or the whole database, is available from Sanderson (hsander@uoguelph.ca).

Stockholm County Council (2005) carried out an environmental hazard assessment of individual pharmaceuticals based on three properties: persistence (P), bioaccumulation (B) and toxicity (T). Each of these properties is assigned a value on a scale of 0 to 3. The sum of the values constitutes the PBT index. PBT index is 0 indicates that the substance is readily biodegradable, not bioaccumulating and has low ecotoxicity. PBT index is 9 indicates that the substance is not readily biodegradable, has potential for bioaccumulation and has very high ecotoxicity. The pharmaceuticals tamoxifen (anti-oestrogen) and ethinylestradiol (sex hormone) for example have a PBT index of 9.

Only 5 pharmaceuticals from the top 20 pharmaceuticals discharged to the DCZ (Table 3) are classified by the Stockholm County Council (2005). The PBT index of carbamazepine, sulfamethoxazole, diclofenac, metoprolol and ibuprofen is respectively 4, 3, 7, 4 and 5. Diclofenac has the highest PBT index. This pharmaceutical is very resistant (not readily biodegradable), bioaccumulates and is moderately toxic (LC/EC/IC50 10-100mg/l). Only three pharmaceuticals mentioned in this study have a PBT index of 9. These pharmaceuticals are propranolol, norfloxacin and tamoxifen.

Unfortunately the x-ray contrast media, which are most ubiquitously present in Dutch surface-, sewage- and industrial water, are not classified by Stockholm County Council (2005). However, Steger-Hartman *et al.* (1998, 1999) outlined that sublethal effect to organisms in the environment are unknown. No toxic effects to *Daphnia magna* were observed using the chronic reproduction test with concentration up to 1 g/l, nor were toxic effects to bacteria (*Vibrio*

Fisheri, *Pseudomonas putida*), algae (*Scenedesmus subspicatus*), crustaceans (*Daphnia magna*) and fish (*Danio rerio*, *Leuciscus*) noted in short-term acute ecotoxicological test systems containing up to 10 g/l of iopromide. Although it is unlikely that X-ray contrast media pose an immediate threat to the environment, their relatively high concentrations, highly persistent nature and unknown sublethal effects urges for further environmental assessment.

It falls outside the scope of this research to discuss the environmental risks of the studied pharmaceuticals. However, it is stated that future research should, besides monitoring of pharmaceutical loads, focus on risk assessment of the discharged pharmaceuticals to coastal zones in order to determine environmental hazards of pharmaceuticals to the coastal and marine ecosystems.

5 Conclusions

In relation to the aim of this research we can conclude the following:

1. All public data on pharmaceutical concentrations in surface-, sewage- and industrial water in the Netherlands has been gathered and listed in a database, which is available at RIKZ. The database comprises over 100 pharmaceuticals, both human and veterinary, which have been measured in the period 1996 and 2005.
2. Pharmaceutical concentrations (>LOD) in surface water in the Netherlands between 1996 and 2005 range from several pg/l (0.02 ng/l oxolinic acid) to several hundred ng/l (830 ng/l diclofenac). The highest median concentrations in surface waters are observed for the X-ray contrast media, with median concentrations ranging from 25 to 145 ng/l. Pharmaceutical concentrations in the northern provinces are in general lower than in the southern provinces. It is however noted that the main rivers are situated in the southern provinces and that most surface water samples are therefore taken in the southern provinces. Highest concentrations are measured in the surface waters from the main rivers (Rhine, Meuse, Schelde, Amsterdam Rijnkanaal).
3. Pharmaceutical concentrations (>LOD) in sewage water in the Netherlands in 2002 range from several ng/l (11 ng/l dimetridazol) to several µg/l (10 µg/l iomeprol). The highest median concentrations in surface waters are observed for the X-ray contrast media, with median concentrations ranging from 190 to 3100 ng/l. Pharmaceutical concentrations in sewage water effluents are in general higher than in surface water.
4. Pharmaceutical concentrations (>LOD) in industrial wastewater in the Netherlands in 2002 range from several ng/l (11 ng/l terbutalin) to a few mg/l (1.1 mg/l iohexol). The highest median concentrations in industrial wastewater are observed for the X-ray contrast media, with median concentrations ranging from 540 ng/l to 665 µg/l. Pharmaceutical concentrations in industrial wastewater are in general higher than in surface water and sewage water effluents.
5. In 2002, riverine discharge to the DCZ for individual pharmaceuticals varied from 0 to 27 ton/year. The discharge of 75% percent of all analysed pharmaceuticals was lower than 2 ton/year. Highest loads were calculated for the X-ray contrast media, e.g. with values in the range of 18 to 27 ton/year for iopromide.

-
6. The direct discharge (sum of sewage water and industrial water) of pharmaceuticals to the DCZ in 2002 for individual pharmaceuticals varied from 0 to 0.27 ton/year for sewage water and from 0 to 0.327 ton/year for industrial wastewater. Highest loads were calculated for sotalol (beta blocker) and diatrizoic acid (X-ray contrast medium) in sewage water and industrial wastewater respectively. The discharge of pharmaceuticals to the DCZ due to direct discharge is negligible low compared to riverine discharge. It determines only from 0 to 5 % of the total discharge of pharmaceuticals to the DCZ.
 7. The top 20 pharmaceuticals discharged to the DCZ is dominated by the X-ray contrast media (iopromide, diatrizoic acid, iopamidol, iomeprol, iohexol, iothalamic acid, ioxithalamic acid), followed by antibiotics (sulfamethoxazol, anhydro-erythromycin, azithromycin, lincomycin, clarithromycin, roxithromycin), analgesics/antipyretics/anti-inflammatory drugs (diclofenac, ibuprofen), beta blockers (sotalol, metoprolol), fibrates/lipid regulators (bezafibrate), veterinary antibiotics (dimetridazol) and others (carbamazepine). The discharge of these pharmaceuticals to the DCZ in 2002 is in the same order of magnitude as the discharge of the mandatory OSPAR substances cadmium (8.8-10 ton/year) and mercury (3.3 ton/year) and higher than the discharge of the mandatory substance lindane (0.041 to 0.055 ton/year) and the recommended substance PCBs (0.217 ton/year) in 2002.
 8. Although some pharmaceuticals are discharged in significant amounts to the DCZ, the human and ecotoxicological risks are largely unknown. To determine the environmental risks of discharged pharmaceuticals to the marine environment, future research should –besides monitoring of loads- focus on risk assessment of the discharged pharmaceuticals.

References

- Barreveld, H.L., Berbee, R.P.M. en Ferdinandy, M.M.A. (2001). 'Vergeten' stoffen in Nederlands oppervlaktewater. RIZA rapport 2001.020.
- Belfroid, A.C., Van der Horst, A., Vethaak, A.D., Schäfer, A.J., Rijs, G.B.J., Wegener, J. and Cofino, W.P. (1999). Analysis and occurrence of estrogenic hormones and their glucuronides in surface water and waste water in The Netherlands. *Sci. Total Environ.* 225, 101-108.
- Blom, A.Th.G., de Bruijn, J.C.M.J. and de Jong, J.G.A.M. (1995). Verspilling. Faculteit Pharmacie, Universiteit Utrecht, Utrecht, The Netherlands.
- Buser, H.R., Muller, M.D. and Theobald, N. (1998^a). Occurrence of the pharmaceutical drug clofibric acid and the herbicide mecoprop in various swiss lakes and in the North Sea. *Environ. Sci. Technol.* 32, 188-192.
- Buser, H.R., Poiger, T. and Muller, M.D. (1998^b). Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: Rapid photodegradation in a lake. *Environ. Sci. Technol.* 32, 3449-3456.
- Buser, H.R., Poiger, T. and Muller, M.D. (1999). Occurrence and environmental behaviour of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. *Environ. Sci. Technol.* 33, 2529-2535.
- Comoretto, L. and Chiron, S. (2005). Comparing pharmaceutical and pesticide loads into a small Mediterranean river. *Sci. Total Environ.* 349, 201-210.
- Derksen, J.G.M., van Eijnatten, G.M., Lahr, J., van der Linde, P. en Kroon, A.G.M. (2001).
- Milieu-effecten van humane geneesmiddelen. RIZA rapport 2001.051.
- Fent, K., Weston, A.A. and Caminada, D. (2005). Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology* (accepted).
- Hamscher, G., Pawelzick, H.T., Nau, H. and Hartung, J. (2002). Detection of antibiotics in dust originating from pig farms. In: *Proceedings of the 21th SETAC Europe Meeting, Vienna, 2002.* SETAC Europe, Brussels, Belgium, p11.
- Hartig, C., Storm, T. and Jekel, M. (1999). Detection and identification of sulphonamide drugs in municipal waste water by liquid chromatography coupled with electrospray ionisation tandem mass spectrometry. *J. Chromatography A* 854, 163-173.
- Hartmann, A., Alder, A.C., Koler, T. and Widmer, R.M. (1998). Identification of fluoroquinolone antibiotics as the main source of umuC genotoxicity in native hospital wastewater. *Environ. Toxicol. Chem.* 17, 377-382.
- Heberer, T. (2002). Occurrence, fate and removal of pharmaceutical residues in the aquatic environment: a review of recent data. *Toxicol. Lett.* 131, 5-17.

-
- Highnate, C., and Azarnoff, D.L. (1977). Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. *Life Sci.* 20, 337-342.
- Hirsch, R., Ternes, T.A., Haberer, K. and Kratz, K. (1996). Determination of betablockers and β -sympathomimetics in the aquatic environment. *Vom Wasser* 87, 263-274.
- Hirsch, R., Ternes, K., Haberer, K and Kratz, . (1999). Ocuence of antibiotics in the aquatic environment. *Sci. Total. Environ.* 225: 109-118.
- Jørgenson, S.E. and Halling-Sørensen, B. (2000). Editorial: drugs in the environment. *Chemosphere* 40, 691-699.
- Klijnsstra, J.W. (2005). Korte bureaustudie naar het voorkomen van farmaceutica in antifoulingsverven. TNO-rapport CA05.8057.
- Mons, M.N., van Genderen, J. and van Dijk-Looijaard, A.M. (2000). Inventory of the presence of pharmaceuticals in Dutch water. KIWA rapport WR6, Nieuwegein, The Netherlands.
- Mons, M.N., Hogenboom, A. and Noij, T.H.M. (2003). Pharmaceuticals and drinking water supply in the Netherlands. KIWA report nr BTO 2003.040, Nieuwegein, The Netherlands.
- OSPAR (2004). Overview of the results of the comprehensive study on riverine inputs and direct discharges (RID) from 2000 to 2002, ISBN 1-904426-58-1.
- Peterson, S.M., Batley, G.E. and Scammell, M.S. (1993). Tetracycline in antifouling paints. *Mar. Pollut. Bull.* 26 (2), 96-100.
- Richardson, M.L. and Bowron, J.M. (1985). The fate of pharmaceutical chemicals in the aquatic environment. *J. Pharm. Pharmacol.* 37, 1-12.
- Rijs, G.B.J., Laane R.W.P.M. en de Maagd, G-J. (2003). Voorkomen is beter dan genezen. Een beleidsanalyse over 'geneesmiddelen en watermilieu', RIZA rapport 2003.037, Lelystad, The Netherlands.
- Rogers, I.H., Birtwell, I.K., Kruzynski, G.M. (1986). Organic extractables in municipal wastewater, Vancouver, British Columbia. *Water Pollut. Res. J. Can.* 21, 187-204.
- Sacher, F. en Stoks, P. (2003). Pharmaceutical residues in waters in the Netherlands. Results of a monitoring programme for RIWA. RIWA report, ISBN 90-6683-106-5, Nieuwegein, The Netherlands.
- Sanderson, H., Johnson, D.J., Reitsma, T., Brain, R.A., Wilson, C.J. and Solomon, K.R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory toxicology and pharmacology* 39, 158-83.
- Schrap, S., Rijs, G.B.J., Beek, M.A., Maaskant, J.F.N., Staeb, J., Stroomberg, G. en Tiesnitsch, J. (2003). Humane en veterinaire geneesmiddelen in Nederlands oppervlaktewater en afvalwater. RIZA rapport 2003.023, Lelystad, The Netherlands.
- Stan, H-J., Linkerhägner, M. (1992). Identifizierung von 2-(4-Chlorphenoxy)-2-methyl-propionsäure im Grundwasser mittels Kapillar-Gaschromatographie mot Atomemissionsdetektion und Massenspektrometrie, *Vom Wasser* 79, 75-88.

-
- Stan, H-J., Heberer, T. and Linkerhägner, M. (1994). Occurrence of clofibric acid in the aquatic system – Is the use in human medical care the source of the contamination of surface, ground, and drinking water? *Vom Wasser* 83, 57-68.
- Stan, H-J. and Heberer, T. (1996). Occurrence of polar organic contaminants in Berlin drinking water. *Vom Wasser* 86, 19-31.
- Steger-Hartmann, Th. Länge, K. and Schweinfurth, H. (1998). Umweltverhalten und ökotoxikologische Bewertung. von iodhaltigen Röntgenkontrastmitteln. *Vom Wasser* 91, 185-194.
- Steger-Hartmann, Th. Länge, K. and Schweinfurth, H. (1998). Environmental risk assessment for the widely used iodinated x-ray contrast agent iopromide (Ultravist). *Ecotoxicology and Environmental Safety* 423, 274-281.
- Stockholm County Council (2005). Environmentally classified pharmaceuticals (www.janusinfo.se).
- Stumpf, M., Ternes, T.A., Haberer, K., Seel, P. and Baumann, W. (1996). *Sci. Tot. Environ.* 225, 135-141.
- Ternes, .A. (1998). Occurrence of drugs in German sewage treatment plants and rivers. *Water research* 32 (11), 3245-3260.
- Ternes, T.A. and Hirsch, R. (2000). Occurrence and behaviour of X-ray contrast media in sewage facilities and the aquatic environment. *Environ. Sci. Technol.* 34, 2741-2748.
- Tixier, C., Singer, H., Oellers, S., Müller, S. (2003). Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen and naproxen in surface waters. *Environ. Sci. Technol.* 37 (6), 1061-1068.
- Versteegh, J.F.M., Stolker, A.A.M., Niesing, W. en Muller, J.J.A. (2003). Geneesmiddelen in drinkwater en drinkwaterbronnen. Resultaten van meetprogramma 2002. RIVM rapport 703719004/2003, Bilthoven, The Netherlands.
- Vethaak, A.D., Rijs, G.B.J., Schrap, S.M., Ruiter, H., Gerritsen, A. and Lahr, J. (2002). Estrogens and xeno-estrogens in the aquatic environment of The Netherlands. Occurrence, potency, and biological effects. RIZA/RIKZ report no. 2002.001, Lelystad, The Netherlands.
- Weigel, S. (2003). Occurrence, distribution and fate of pharmaceuticals and further polar contaminants in the marine environment. Dissertation Universität Hamburg.
- Weigel, S., Berger, U., Jensen, E., Kallenborn, R., Thoresen, H. and Hühnerfuss, H. (2004). Determination of selected pharmaceuticals and caffeine in sewage and sewer water from Tromsø/Norway with emphasis on ibuprofen and its metabolites. *Chemosphere* 56, 583-592.
- Weil, H. and Knepper, T.P. (2006). Pharmaceuticals in the River Rhine. In: The Rhine, T.P. Knepper (ed.). *The Handbook of Environmental Chemistry vol. 5: Water Pollution Part C*, Springer Verlag, Berlin, 177-184.

Appendices

Appendix A Consulted libraries, databases, websites and keywords

Libraries

- University of Utrecht

Databases

- GeoRef
- Chemical Abstracts

Websites

- www.google.nl
- www.irdes.fr/ecosante/OCDE
- www.janusinfo.se
- www.cbs.nl
- www.epa.gov
- www.stowa.nl
- www.rivm.nl
- www.riwa.org
- www.riza.nl
- www.wlba.amsterdam.nl

Keywords

- Pharmaceuticals, surface, sewage, industrial, water, wastewater, load, calculation, North Sea, Netherlands, toxicity, physical, chemical, properties, OSPAR, flow, rate, STP, removal, rates, efficiency, databases.

Appendix B Median concentrations (ng/l) of 7 pharmaceuticals in surface water in the Netherlands in 2002, calculated according to method 1

**Monsterlocaties
2002**

**Oxytetracyclin
2002**

**Dimetridazol
2002**

**Diclofenac
2002**

**Iopromide
2002**

**Bezafibrate
2002**

**Sotalol
2002**

**Carbamazepine
2002**

Location	Abbreviation
Andijk	AND
Barneveldse beek	BAR
Bethunepolder	BTP
Drentse Aa	DAA
Eysden	EYS
Haringvliet	HAR
Heel Lateraalkanaal	HEE
Keizersveer	KEI
Ketelmeer	KET
KrommeRijn	KROM
Lobith	LOB
Lunterse beek	LUN
Maassluis	MAA
Brakel afgedamde Maas	MAB
Maas Roosteren	MAR
Nieuwegein	NGN
Naardermeer	NRD
Amsterdamrijnkanaal (Nieuwersluis)	NSL
Peelkanaal	PKN
De Punt	PNT
Schaar v Ouden Doel	SOD
Tovensche Beek	TVB
Twentekanaal	TWK

Appendix C.1 Flow rate versus concentrations of carbamazepine, diclofenac, iopromide and bezafibrate in the Rhine near Lobith (data from 1999-2005).

Appendix C.2 Flow rate and concentrations of carbamazepine, diclofenac, iopromide and bezafibrate versus time in the Rhine near Lobith

Appendix D Pharmaceutical loads (ton/year) in the Netherlands in 2002

Riverine input of pharmaceuticals to the Netherlands from neighbouring countries

Group	Pharmaceuticals-metabolites	n	Method 1			Method 2		
			range	median	average	Range	median	average
			ton/year			ton/year		
Antibiotics	Amoxicillin	5	0,00 - 0,16	0,08	0,08	1,08 - 1,13	1,11	1,11
	Ampicillin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Anhydro-erythromycin	5	1,81 - 2,60	2,21	2,21	1,92 - 2,60	2,26	2,26
	Azithromycin	2	2,20 - 2,20	2,20	2,20	2,20 - 2,20	2,20	2,20
	Cefaclor	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Cefadroxil	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Cefalexin	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Cefixim	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Ceftiofur	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Ceftriaxon	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Cefuroxim	2	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Chlooramfenicol	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Chloortetracyclin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Ciprofloxacin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Clarithromycin	5	0,59 - 1,81	1,20	1,20	0,62 - 1,84	1,23	1,23
	Clindamycin	5	0,10 - 1,14	0,62	0,62	1,15 - 1,25	1,20	1,20
	Cloxacillin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Dapson	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Dicloxacillin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Doxycyclin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Enoxacin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Enrofloxacin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Erythromycin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Flumequin	5	0,01 - 0,14	0,08	0,08	0,09 - 0,14	0,12	0,12
	Furazolidon	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Lincomycin	5	0,05 - 0,06	0,05	0,05	0,10 - 0,10	0,10	0,10
	Meclocyclin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Metronidazol	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Nafcillin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Norfloxacin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Ofloxacin	5	0,00 - 0,27	0,14	0,14	1,08 - 1,24	1,16	1,16
	Oleandomycin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Oxacillin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Oxolinic acid	5	0,00 - 0,00	0,00	0,00	0,12 - 0,12	0,12	0,12
	Oxytetracyclin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Penicillin G	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Penicillin V	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Ronidazol	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Roxitromycin	5	0,55 - 2,01	1,28	1,28	0,68 - 2,03	1,36	1,36
	Spiramycin	5	0,00 - 0,16	0,08	0,08	1,08 - 1,13	1,11	1,11
	Sulfachloor pyridazine	5	0,00 - 0,00	0,00	0,00	0,11 - 0,11	0,11	0,11
	Sulfadiazine	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Sulfadimethoxine	5	0,00 - 0,07	0,04	0,04	0,04 - 0,07	0,06	0,06
	Sulfadimidine	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Sulfamerazin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Sulfamethoxazol	5	1,94 - 3,55	2,74	2,74	1,94 - 3,55	2,74	2,74
	Sulfaguinoxaline	5	0,00 - 0,00	0,00	0,00	0,06 - 0,06	0,06	0,06
	Tetracycline	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Trimethoprim	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Tylosin	5	0,00 - 0,00	0,00	0,00	0,06 - 0,06	0,06	0,06
	Virginiamycin	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
Anthelmintic	Mebendazol	5	0,01 - 0,02	0,02	0,02	0,02 - 0,02	0,02	0,02
Veterinary antibiotics	Dimetridazol	5	0,14 - 1,53	0,83	0,83	0,15 - 1,53	0,84	0,84
	Monensin	5	0,00 - 0,63	0,31	0,31	0,53 - 0,64	0,59	0,59
Analgesics / antipyretics and anti-inflammatory	Narasin	5	0,00 - 0,24	0,12	0,12	0,14 - 0,24	0,19	0,19
	Acetylsalicylic acid	5	0,53 - 2,00	1,27	1,27	0,53 - 2,00	1,27	1,27
	Aminofenazon	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Diclofenac	5	5,86 - 15,23	10,55	10,55	5,86 - 15,23	10,55	10,55
	Fenazon	5	0,00 - 0,94	0,47	0,47	1,08 - 1,08	1,08	1,08
	Fenoprofen	5	0,00 - 0,47	0,24	0,24	1,08 - 1,44	1,26	1,26
	Ibuprofen (methode 1)	5	0,51 - 2,18	1,34	1,34	0,53 - 2,18	1,35	1,35
	Ibuprofen (methode 3)	0	0,00 - 0,00	0,00	0,00	0,00 - 0,00	0,00	0,00
	Indomethacin	5	0,08 - 0,08	0,08	0,08	1,13 - 1,13	1,13	1,13
	Ketoprofen	5	0,00 - 0,29	0,14	0,14	1,08 - 1,26	1,17	1,17
	Naproxen	5	0,62 - 0,93	0,77	0,77	1,56 - 1,87	1,72	1,72
	Paracetamol	5	0,20 - 1,72	0,96	0,96	0,21 - 1,72	0,97	0,97
	Propyphenazone	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
X-ray contrast media	Diatrizoic acid	5	8,59 - 21,93	15,26	15,26	8,59 - 21,93	15,26	15,26
	Iodipamide	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Iohexol	5	4,89 - 8,66	6,77	6,77	4,89 - 8,66	6,77	6,77
	Iomeprol	5	5,21 - 9,67	7,44	7,44	5,32 - 9,67	7,50	7,50
	Iopamidol	5	12,25 - 18,97	15,61	15,61	12,39 - 18,99	15,69	15,69
	Iopanoic acid	5	0,00 - 0,00	0,00	0,00	1,08 - 1,08	1,08	1,08
	Iopromide	5	15,54 - 69,91	42,73	42,73	15,54 - 69,91	42,73	42,73
	Iothalamic acid	5	0,27 - 6,36	3,31	3,31	1,32 - 6,36	3,84	3,84
	Ioxaglinic acid	5	0,14 - 2,56	1,35	1,35	1,19 - 3,50	2,35	2,35
	Ioxithalamic acid	5	2,45 - 3,12	2,79	2,79	2,45 - 3,12	2,79	2,79

Group	Pharmaceuticals- metabolites	n	Method 1					Method 2				
			range			median	average	Range			median	average
			ton/year					ton/year				
Fibrates / lipid regulators	Bezafibrate	5	0,21	-	1,63	0,92	0,92	1,26	-	1,63	1,45	1,45
	Clofibrac acid	5	0,00	-	1,41	0,71	0,71	1,08	-	1,55	1,32	1,32
	Etofibrate	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Fenofibrate	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Fenofibric acid	5	0,25	-	0,27	0,26	0,26	1,22	-	1,24	1,23	1,23
	Gemfibrozil	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Simvastatin	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Pentoxiphylline	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
Beta blockers	Atenolol	5	1,47	-	2,16	1,82	1,82	1,47	-	2,16	1,82	1,82
	Betaxolol	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Bisoprolol	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Metoprolol	5	2,20	-	2,86	2,53	2,53	2,31	-	2,97	2,64	2,64
	Pindolol	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Propranolol	5	0,00	-	0,16	0,08	0,08	1,08	-	1,13	1,11	1,11
	Sotalol	5	7,55	-	10,55	9,05	9,05	7,55	-	10,55	9,05	9,05
Bronchitis and asthma	Salbutamol	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Terbutalin	5	0,00	-	0,03	0,01	0,01	0,09	-	0,11	0,10	0,10
Antineoplastics	Cyclophosphamide	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Ifosfamide	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
	Carbamazepine	5	7,01	-	7,92	7,47	7,47	7,01	-	7,92	7,47	7,47
	Primidon	5	0,83	-	1,77	1,30	1,30	0,85	-	1,77	1,31	1,31
Anti-oestrogen	Tamoxifen	5	0,00	-	0,01	0,00	0,00	0,06	-	0,07	0,07	0,07
Neuroleptics	Diazepam	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
Anaesthetics	Lidocaine	5	0,26	-	0,95	0,61	0,61	0,26	-	0,95	0,61	0,61
Steroids	Clenbuterol	5	0,00	-	0,00	0,00	0,00	1,08	-	1,08	1,08	1,08
Antifungal veterinary drug	Malachite green oxalate	3	0,01	-	0,01	0,01	0,01	0,01	-	0,01	0,01	0,01

Riverine discharge of pharmaceuticals (ton/year) to DCZ

Group	Pharmaceuticals- metabolites	n	Method 1					Method 2				
			range			median	average	Range			median	average
			ton/year					ton/year				
Antibiotics	Amoxicillin	8	0,00	-	0,00	0,00	0,00	3,31	-	3,31	3,31	3,31
	Ampicillin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Anhydro-erythromycin	2	1,21	-	3,86	2,53	2,53	1,21	-	3,86	2,53	2,53
	Azithromycin	2	2,09	-	2,09	2,09	2,09	2,09	-	2,09	2,09	2,09
	Cefaclor	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Cefadroxil	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Cefalexin	8	0,00	-	0,00	0,00	0,00	3,31	-	3,31	3,31	3,31
	Cefixim	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ceftiofur	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ceftriaxone	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Cefuroxim	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Chloramphenicol	5	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Chlortetracycline	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ciprofloxacin	8	0,00	-	0,00	0,00	0,00	6,06	-	6,06	6,06	6,06
	Clarithromycin	2	0,00	-	2,42	1,21	1,21	1,10	-	2,42	1,76	1,76
	Clindamycin	2	0,00	-	1,21	0,61	0,61	1,10	-	1,21	1,16	1,16
	Cloxacillin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Dapson	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Dicloxacillin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Doxycycline	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Enoxacin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Enrofloxacin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Erythromycin	11	0,00	-	0,50	0,00	0,12	1,27	-	6,06	6,06	4,45
	Flumequin	8	0,06	-	0,85	0,17	0,31	0,34	-	0,56	0,45	0,45
	Furazolidon	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Lincomycin	8	0,00	-	2,64	1,32	1,32	0,08	-	2,70	1,39	1,39
	Meclocycline	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Metronidazol	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Nafcillin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Norfloxacin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ofloxacin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Oleandomycin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Oxacillin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Oxolinic acid	8	0,00	-	0,00	0,00	0,00	0,34	-	0,34	0,34	0,34
	Oxytetracycline	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Penicillin G	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Penicillin V	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ronidazol	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Roxithromycin	2	0,00	-	2,20	1,10	1,10	1,10	-	2,20	1,65	1,65
	Spiramycin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Sulfachlor pyridazine	8	0,00	-	0,00	0,00	0,00	0,33	-	0,33	0,33	0,33
	Sulfadiazine	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Sulfadimethoxine	8	0,02	-	0,02	0,02	0,02	0,08	-	0,08	0,08	0,08
	Sulfadimidine	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Sulfamerazin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Sulfamethoxazol	11	2,77	-	8,99	5,24	5,56	2,77	-	8,99	5,21	5,49
	Sulfaquinoxaline	8	0,00	-	1,53	0,00	0,38	0,09	-	0,09	0,09	0,09
	Tetracycline	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Trimethoprim	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Tylosin	8	0,00	-	0,00	0,00	0,00	0,09	-	0,09	0,09	0,09
	Virginiamycin	2	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
Anthelmintic	Mebendazol	8	0,00	-	0,01	0,01	0,01	0,03	-	0,04	0,04	0,04

Group	Pharmaceuticals- metabolites	n	Method 1					Method 2				
			range		median	average		Range		median	average	
			ton/year					ton/year				
Veterinary antibiotics	Dimetridazol	8	1,16	-	2,97	2,07	2,07	1,43	-	3,25	2,34	2,34
	Monensin	8	0,00	-	0,00	0,00	0,00	0,82	-	0,82	0,82	0,82
	Narasin	8	0,00	-	0,15	0,08	0,08	0,34	-	0,43	0,38	0,38
Analgesics / antipyretics and anti-inflammatory	Acetylsalicylic acid	11	0,20	-	1,27	0,74	0,74	0,48	-	2,69	1,01	1,30
	Aminofenazon	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Diclofenac	11	2,75	-	4,88	3,98	3,90	3,31	-	5,10	4,05	4,07
	Fenazon	8	0,00	-	0,26	0,00	0,09	1,10	-	1,15	1,10	1,12
	Fenoprofen	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ibuprofen (methode 1)	11	0,77	-	4,38	2,34	2,46	1,32	-	4,60	2,89	2,92
	Ibuprofen (methode 3)	0		-					-			
	Indomethacin	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ketoprofen	8	0,00	-	0,55	0,28	0,28	1,10	-	1,10	1,10	1,10
	Naproxen	8	0,00	-	1,32	0,66	0,66	1,10	-	1,87	1,49	1,49
	Paracetamol	11	0,15	-	0,48	0,32	0,32	0,43	-	1,04	0,59	0,69
	Propyphenazone	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
X-ray contrast media	Diatrizoic acid	6	5,59	-	12,38	8,99	8,99	5,59	-	12,38	8,99	8,99
	Iodipamide	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Iohexol	6	3,92	-	5,35	4,64	4,64	3,92	-	5,35	4,64	4,64
	Iomeprol	6	5,19	-	7,64	6,42	6,42	5,19	-	7,64	6,42	6,42
	Iopamidol	6	4,88	-	12,81	8,84	8,84	4,88	-	12,81	8,84	8,84
	Iopanoic acid	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Iopromide	6	18,45	-	26,77	22,61	22,61	18,45	-	26,77	22,61	22,61
	Iothalamic acid	8	0,00	-	3,69	1,85	1,85	1,10	-	4,24	2,67	2,67
	Ioxaglinic acid	7	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ioxithalamic acid	6	0,00	-	1,79	0,89	0,89	1,10	-	2,01	1,55	1,55
	Bezafibrate	11	0,00	-	3,59	1,26	1,53	1,04	-	4,13	2,78	2,59
	Clofibrac acid	11	0,00	-	1,57	0,36	0,59	1,00	-	1,57	1,18	1,23
Fibrates / lipid regulators	Etofibrate	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Fenofibrate	11	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Fenofibrac acid	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Gemfibrozil	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Simvastatin	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Pentoxiphylline	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Atenolol	8	0,00	-	1,09	0,70	0,60	1,10	-	1,31	1,19	1,20
	Betaxolol	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
Beta blockers	Bisoprolol	11	0,00	-	0,23	0,00	0,06	1,00	-	1,10	1,10	1,08
	Metoprolol	11	0,00	-	4,85	2,81	2,65	1,10	-	4,85	3,08	3,04
	Pindolol	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Propranolol	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Sotalol	8	3,96	-	6,66	4,63	5,09	4,18	-	6,66	4,85	5,23
Bronchitis and asthma	Salbutamol	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Terbutalin	8	0,00	-	0,00	0,00	0,00	0,59	-	0,59	0,59	0,59
Antineoplastics	Cyclophosphamide	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Ifosfamide	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
	Carbamazepine	16	1,49	-	22,15	12,06	11,68	3,37	-	22,15	12,76	12,77
	Primidon	8	0,35	-	3,95	0,53	1,34	0,63	-	0,99	0,81	0,81
Anti-oestrogen	Tamoxifen	8	0,00	-	0,00	0,00	0,00	0,09	-	0,09	0,09	0,09
Neuroleptics	Diazepam	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
Anaesthetics	Lidocaine	8	0,10	-	0,52	0,31	0,31	0,13	-	0,55	0,34	0,34
Steroids	Clenbuterol	8	0,00	-	0,00	0,00	0,00	1,10	-	1,10	1,10	1,10
Antifungal veterinary drug	Malachite green oxalate	7	0,01	-	0,01	0,01	0,01	0,07	-	0,07	0,07	0,07

Direct discharge of pharmaceuticals with sewage water effluents to DCZ

Group	Pharmaceuticals- metabolites	n	Method 1				Method 2					
			range		median	average	range		median	average		
			ton/year				ton/year					
Antibiotics	Amoxicillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ampicillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Anhydro-erytromycin	7	0,03	-	0,09	0,05	0,05	0,03	-	0,09	0,05	0,05
	Azithromycin	4	0,02	-	0,06	0,03	0,04	0,02	-	0,06	0,03	0,04
	Cefaclor	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Cefadroxil	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Cefalexin	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Cefixim	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Ceftiofur	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Ceftriaxon	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Cefuroxim	4	0,00	-	0,00	0,00	0,00	0,01	-	0,01	0,01	0,01
	Chlooramfenicol	7	0,00	-	0,01	0,00	0,00	0,01	-	0,02	0,01	0,01
	Chloortetracyclin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ciprofloxacin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Clarithromycin	7	0,02	-	0,06	0,04	0,04	0,02	-	0,06	0,04	0,04
	Clindamycin	7	0,00	-	0,03	0,01	0,01	0,00	-	0,03	0,01	0,01
	Cloxacillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Dapson	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Dicloxacillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Doxycyclin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Enoxacin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Enrofloxacin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Erytromycin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Flumequin	7	0,00	-	0,49	0,00	0,07	0,00	-	0,49	0,00	0,07
	Furazolidon	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Lincomycin	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
	Meclocyclin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Metronidazol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Nafcillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Norfloxacin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ofloxacin	7	0,00	-	0,02	0,01	0,01	0,00	-	0,02	0,01	0,01
	Oleandomycin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Oxacillin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Oxolinic acid	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
	Oxytetracyclin	7	0,00	-	0,08	0,00	0,01	0,01	-	0,08	0,01	0,02
	Penicillin G	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
Penicillin V	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Ronidazol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Roxitromycin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Spiramycin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Sulfachloor pyridazine	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00	
Sulfadiazine	7	0,00	-	0,01	0,00	0,00	0,01	-	0,02	0,01	0,01	
Sulfadimethoxine	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00	
Sulfadimidine	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Sulfamerazin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Sulfamethoxazol	7	0,01	-	0,02	0,02	0,02	0,01	-	0,02	0,02	0,02	
Sulfaquinoxaline	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00	
Tetracycline	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Trimethoprim	7	0,01	-	0,02	0,02	0,02	0,01	-	0,02	0,02	0,02	
Tylosin	7	0,00	-	0,02	0,00	0,00	0,00	-	0,02	0,00	0,00	
Virginiamycin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01	
Anthelmentic	Mebendazol	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
Veterinary antibiotics	Dimetridazol	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
	Monensin	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
	Narasin	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
Analgesics / antipyretics and anti-inflammatory	Acetylsalicylic acid	7	0,00	-	0,01	0,01	0,01	0,00	-	0,01	0,01	0,01
	Aminofenazon	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Diclofenac	7	0,07	-	0,15	0,09	0,09	0,07	-	0,15	0,09	0,09
	Fenazon	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Fenoprofen	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ibuprofen (methode 1)	7	0,02	-	0,13	0,05	0,06	0,02	-	0,13	0,05	0,06
	Ibuprofen (methode 3)	7	0,00	-	0,06	0,01	0,02	0,00	-	0,06	0,01	0,02
	Indomethacin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ketoprofen	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Naproxen	7	0,03	-	0,22	0,05	0,08	0,03	-	0,22	0,05	0,08
	Paracetamol	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
	Propyphenazone	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
X-ray contrast media	Diatrizoic acid	7	0,04	-	0,20	0,05	0,09	0,04	-	0,20	0,05	0,09
	Iodipamide	7	0,00	-	0,00	0,00	0,00	0,02	-	0,02	0,02	0,02
	Iohexol	7	0,00	-	0,64	0,02	0,12	0,00	-	0,64	0,02	0,12
	Iomeprol	7	0,00	-	1,68	0,03	0,39	0,00	-	1,68	0,03	0,39
	Iopamidol	7	0,00	-	0,00	0,00	0,00	0,02	-	0,02	0,02	0,02
	Iopanoic acid	7	0,00	-	0,00	0,00	0,00	0,02	-	0,02	0,02	0,02
	Iopromide	7	0,00	-	0,09	0,00	0,02	0,02	-	0,09	0,02	0,03
	Iothalamic acid	7	0,00	-	0,14	0,03	0,03	0,00	-	0,14	0,03	0,03
	Ioxaglinic acid	7	0,00	-	0,00	0,00	0,00	0,02	-	0,02	0,02	0,02
	Ioxithalamic acid	7	0,00	-	0,12	0,03	0,05	0,00	-	0,12	0,03	0,05
Fibrates / lipid regulators	Bezafibrate	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
	Clofibric acid	7	0,00	-	0,02	0,00	0,00	0,01	-	0,02	0,02	0,01
	Etofibrate	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
	Fenofibrate	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
	Fenofibric acid	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
	Gemfibrozil	7	0,04	-	0,20	0,10	0,10	0,04	-	0,20	0,10	0,10
	Simvastatin	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
	Pentoxiphylline	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01

Group	Pharmaceuticals- metabolites	n	Method 1					Method 2				
			range			median	average	range			median	average
			ton/year					ton/year				
Beta blockers	Atenolol	7	0,02	-	0,14	0,09	0,09	0,02	-	0,14	0,09	0,09
	Betaxolol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Bisoprolol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Metoprolol	7	0,05	-	0,17	0,08	0,09	0,05	-	0,17	0,08	0,09
	Pindolol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Propranolol	7	0,00	-	0,02	0,01	0,01	0,00	-	0,02	0,01	0,01
	Sotalol	7	0,16	-	0,27	0,18	0,21	0,16	-	0,27	0,18	0,21
Bronchitis and asthma	Salbutamol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Terbutalin	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
Antineoplastics	Cyclophosphamide	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Ifosfamide	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
	Carbamazepine	7	0,06	-	0,17	0,08	0,10	0,06	-	0,17	0,08	0,10
	Primidon	7	0,00	-	0,01	0,00	0,00	0,00	-	0,01	0,00	0,00
Anti-oestrogen	Tamoxifen	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00
Neuroleptics	Diazepam	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,02	0,01
Anaesthetics	Lidocaine	7	0,00	-	0,02	0,01	0,01	0,00	-	0,02	0,01	0,01
Steroids	Clenbuterol	7	0,00	-	0,00	0,00	0,00	0,01	-	0,02	0,01	0,01
Antifungal veterinary drug	Malachite green oxalate	7	0,00	-	0,00	0,00	0,00	0,00	-	0,00	0,00	0,00

Direct discharge of pharmaceuticals (tons/year) with industrial waste water effluent to DCZ

Group	Pharmaceuticals- metabolites	n	Method 1					Method 2				
			range			median	average	range			median	average
			ton/year					ton/year				
Antibiotics	Amoxicillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Ampicillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,009	0,012
	Anhydro-erythromycin	10	0,000	-	0,024	0,001	0,003	0,025	-	0,087	0,052	0,050
	Azithromycin	6	0,000	-	0,000	0,000	0,000	0,022	-	0,059	0,034	0,037
	Cefaclor	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Cefadroxil	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Cefalexin	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Cefixim	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Ceftiofur	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Ceftriaxon	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Cefuroxim	6	0,000	-	0,000	0,000	0,000	0,008	-	0,008	0,008	0,008
	Chlooramfenicol	10	0,000	-	0,014	0,000	0,002	0,008	-	0,017	0,011	0,012
	Chloortetracyclin	10	0,000	-	0,010	0,000	0,001	0,008	-	0,017	0,008	0,012
	Ciprofloxacin	10	0,000	-	0,524	0,000	0,056	0,008	-	0,017	0,008	0,012
	Clarithromycin	10	0,000	-	0,004	0,000	0,001	0,020	-	0,062	0,042	0,041
	Clindamycin	10	0,000	-	0,070	0,000	0,012	0,000	-	0,034	0,012	0,013
	Cloxacillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Dapson	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Dicloxacillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Doxycyclin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Enoxacin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Enrofloxacin	10	0,000	-	0,089	0,000	0,012	0,008	-	0,017	0,008	0,012
	Erythromycin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Flumequin	10	0,000	-	0,024	0,000	0,003	0,000	-	0,487	0,003	0,072
	Furazolidon	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Lincomycin	10	0,000	-	0,026	0,000	0,005	0,000	-	0,002	0,000	0,000
	Medocyclin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Metronidazol	10	0,000	-	0,008	0,000	0,001	0,008	-	0,017	0,008	0,012
	Nafcillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Norfloxacin	10	0,000	-	0,024	0,000	0,004	0,008	-	0,017	0,008	0,012
	Ofloxacin	10	0,000	-	0,018	0,000	0,002	0,000	-	0,018	0,009	0,007
	Oleandomycin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Oxacillin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Oxolinic acid	10	0,000	-	0,001	0,000	0,000	0,000	-	0,001	0,000	0,000
	Oxytetracyclin	10	0,000	-	0,262	0,000	0,030	0,008	-	0,082	0,009	0,021
	Penicillin G	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Penicillin V	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Ronidazol	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Roxitromycin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Spiramycin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Sulfachloor pyridazine	10	0,000	-	0,000	0,000	0,000	0,000	-	0,002	0,002	0,001
	Sulfadiazine	10	0,000	-	0,072	0,000	0,007	0,007	-	0,017	0,008	0,011
	Sulfadimethoxine	10	0,000	-	0,000	0,000	0,000	0,000	-	0,002	0,002	0,001
	Sulfadimidine	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Sulfamerazin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
	Sulfamethoxazol	10	0,000	-	0,052	0,000	0,005	0,009	-	0,022	0,016	0,015
	Sulfaguinoxaline	10	0,000	-	0,000	0,000	0,000	0,002	-	0,002	0,002	0,002
	Tetracycline	10	0,000	-	0,037	0,000	0,004	0,008	-	0,017	0,008	0,012
	Trimethoprim	10	0,000	-	0,014	0,000	0,003	0,005	-	0,024	0,017	0,017
	Tylosin	10	0,000	-	0,000	0,000	0,000	0,001	-	0,020	0,002	0,004
	Virginiamycin	10	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012
Anthelmintic	Mebendazol	10	0,000	-	0,000	0,000	0,000	0,000	-	0,002	0,001	0,001
Veterinary antibiotics	Dimetridazol	10	0,000	-	0,031	0,000	0,005	0,000	-	0,003	0,001	0,001
	Monensin	10	0,000	-	0,000	0,000	0,000	0,002	-	0,002	0,002	0,002
	Narasin	10	0,000	-	0,000	0,000	0,000	0,000	-	0,002	0,002	0,001

Group	Pharmaceuticals- metabolites	n	Method 1				Method 2						
			range		median	average	range		median	average			
			ton/year				ton/year						
Analgesics / antipyretics and anti-inflammatory	Acetylsalicylic acid	10	0,000	-	0,007	0,000	0,001	0,003	-	0,008	0,006	0,006	
	Aminofenazon	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Diclofenac	6	0,000	-	0,009	0,003	0,004	0,071	-	0,150	0,087	0,094	
	Fenazon	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Fenoprofen	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Ibuprofen (methode 1)	6	0,000	-	0,031	0,009	0,012	0,020	-	0,128	0,049	0,062	
	Ibuprofen (methode 3)	10	0,000	-	0,007	0,000	0,002	0,000	-	0,055	0,006	0,020	
	Indomethacin	6	0,000	-	0,001	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Ketoprofen	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Naproxen	6	0,000	-	0,159	0,035	0,060	0,025	-	0,218	0,049	0,080	
	Paracetamol	10	0,000	-	0,122	0,001	0,029	0,002	-	0,004	0,002	0,002	
	Propyphenazone	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
X-ray contrast media	Diatrizoic acid	6	0,000	-	0,327	0,067	0,109	0,039	-	0,202	0,047	0,086	
	Iodipamide	6	0,000	-	0,000	0,000	0,000	0,017	-	0,017	0,017	0,017	
	Iohexol	6	0,000	-	2,401	0,001	0,424	0,000	-	0,639	0,020	0,119	
	Iomeprol	6	0,000	-	1,659	0,000	0,484	0,000	-	1,680	0,032	0,393	
	Iopamidol	6	0,000	-	0,008	0,000	0,001	0,017	-	0,017	0,017	0,017	
	Iopanoic acid	6	0,000	-	0,000	0,000	0,000	0,017	-	0,017	0,017	0,017	
	Iopromide	6	0,000	-	0,000	0,000	0,000	0,017	-	0,092	0,017	0,029	
	Iothalamic acid	6	0,000	-	0,155	0,006	0,039	0,000	-	0,139	0,030	0,033	
	Ioxaglinic acid	6	0,000	-	0,873	0,000	0,146	0,017	-	0,017	0,017	0,017	
	Ioxithalamic acid	6	0,000	-	2,182	0,013	0,389	0,000	-	0,123	0,032	0,049	
	Fibrates / lipid regulators	Bezafibrate	6	0,000	-	0,001	0,000	0,000	0,008	-	0,017	0,017	0,014
	Clofibric acid	6	0,000	-	0,000	0,000	0,000	0,008	-	0,018	0,017	0,015	
Etofibrate	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,017	0,014		
Fenofibrate	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,017	0,014		
Fenofibric acid	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,017	0,014		
Gemfibrozil	6	0,000	-	0,033	0,001	0,008	0,042	-	0,202	0,097	0,098		
Simvastatin	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,017	0,014		
Pentoxiphylline	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,017	0,014		
Beta blockers	Atenolol	6	0,000	-	0,007	0,003	0,003	0,018	-	0,136	0,089	0,087	
	Betaxolol	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Bisoprolol	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Metoprolol	6	0,000	-	0,003	0,001	0,001	0,054	-	0,166	0,081	0,088	
	Pindolol	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Propranolol	6	0,000	-	0,001	0,000	0,000	0,000	-	0,017	0,011	0,010	
	Sotalol	6	0,000	-	0,008	0,003	0,003	0,163	-	0,269	0,185	0,213	
Bronchitis and asthma	Salbutamol	6	0,000	-	0,007	0,000	0,001	0,008	-	0,017	0,008	0,012	
	Terbutalin	10	0,000	-	0,000	0,000	0,000	0,000	-	0,001	0,000	0,000	
Antineoplastics	Cyclophosphamide	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
	Ifosfamide	6	0,000	-	0,003	0,000	0,001	0,008	-	0,017	0,008	0,012	
	Carbamazepine	6	0,000	-	0,002	0,001	0,001	0,055	-	0,168	0,082	0,099	
	Primidon	10	0,000	-	0,000	0,000	0,000	0,001	-	0,005	0,001	0,002	
Anti-oestrogen	Tamoxifen	10	0,000	-	0,000	0,000	0,000	0,002	-	0,002	0,002	0,002	
Neuroleptics	Diazepam	6	0,000	-	0,001	0,000	0,000	0,008	-	0,017	0,017	0,014	
Anaesthetics	Lidocaine	10	0,000	-	0,022	0,000	0,003	0,003	-	0,020	0,012	0,011	
Steroids	Clenbuterol	6	0,000	-	0,000	0,000	0,000	0,008	-	0,017	0,008	0,012	
Antifungal veterinary drug	Malachite green oxalate	10	0,000	-	0,001	0,000	0,000	0,000	-	0,002	0,002	0,001	