Pharmaceutical Residues in Waters in the Netherlands

Results of a monitoring programme for RIWA

Dr. Frank Sacher, DVGW-Technologiezentrum Wasser (TZW), Karlsruhe

Dr. Peter G Stoks, RIWA, Nieuwegein

November 2003

Association of River Waterworks

RIWA

Summary

As part of the monitoring program of the Association of River Waterworks in the Dutch part of the Rhine catchment area (RIWA) a total of 78 pharmaceuticals including, among others, analgesics, antiepileptics, antibiotica and X-ray contrast media (XRF) were analysed in five different locations during the year 2002. Four of these sampling locations were intake points for drinking water, the fifth location was a site on the Rhine river on the Dutch-German border. In all three locations directly influenced by the Rhine river itself a number of pharmaceuticals could be detected in each sample. In contrast, at the other two locations pharmaceuticals were detected only occasionally. The highest values were found on the German border and at the intake point some 50 miles downstream (up to several hundred nanograms per liter for certain XRF and analgetics) and were markedly lower in the other locations.

Introduction

Several reports have been published during the last few years indicating the presence of pharmaceuticals in surface water, and even in drinking water. These findings triggered the Association of River Waterworks in the Dutch part of the Rhine river, RIWA, to conduct a literature survey *(Derksen J.G.M., G.M. van Eijnatten, J. Lahr, P. van der Linde en A.G.M. Kroon, 2000 - Milieu-effecten van humane geneesmiddelen. Aanwezigheid en risico's. RIWA/RIZA-rapport 2000.051, Amsterdam/Lelystad)* together with the national Water authority in the Netherlands, RIZA. In addition, the Association of River Waterworks in the downstream part of the Rhine in Germany, ARW, initiated a research program in which a broad array of pharmaceuticals was incorporated in the routine monitoring program.

From the literature survey mentioned before, it was obvious that most publications dealt with the situation in Germany, and actual findings in the Netherlands were scarce. Discussions between RIWA and RIZA, as well as the initiatives being taken under the framework of the Dutch national research program of the drinking water utilities (coordinated and conducted by Kiwa), together with the research initiative within the Dutch Institute for Public Health and Environment, RIVM, led to the agreement that each organization would conduct its own program. The emphasis for RIZA being on waste water and surface water, for RIWA being intake points, and for both Kiwa and RIVM being intake points, wells as well as drinking water. A close harmonization was, however, agreed upon in order to avoid overlap. The present report gives the results for the RIWA program.

Materials and Methods

In 2002 samples from different sites relevant for drinking water production in the Netherlands were taken and analysed for a total of 78 pharmaceutical residues including analgesics, antiphlogistics, antirheumatics, beta-blockers, broncholytics, antiepileptics, lipid-lowering agents, vasodilators, tranquillisers, antineoplastic drugs, iodinated x-ray contrast media, and antibiotics of different kind, mainly sulfonamides, macrolides, penicillins, fluoroquinolones and tetracyclines. Also a few metabolites were included. Table 1 presents an overview of the various substances analyzed, classified according to their pharmaceutical mode of action. Beginning in January 2002, grab samples were taken once a month at the German-Dutch border (site *"Bimmen"*), and at several intake points for drinking water: *"WRK Ruw"*, *"WRK III Andijk"*, and *"Bethunepolder"* (from January to March 2002) and *"Inn. Twentekanaal"* (from April to December 2002). The samples were transported to Karlsruhe and analysed for pharmaceutical residues within less than three weeks. The analytical methods used for the determination of the target compounds are described in detail in *Sacher, F., Lange, F.Th., Brauch, H.-J., and Blankenhorn, I.: Pharmaceuticals in groundwaters - Analytical methods and results of a monitoring program in Baden-Württemberg, Germany. J. Chromatogr.* A 938 (1-2), 199-210 (2001).

Results

A total of 45 samples were analysed. Out of 78 pharmaceuticals, 24 could be detected in at least one sample in a concentration above the limit of detection which was 10 ng/L for all compounds under investigation. In all of the samples directly influenced by the Rhine river itself *("Bimmen", "WRK Ruw",* and *"WRK III Andijk")* several pharmaceutical residues were found, whereas in samples *"Bethune-polder"* and *"Inn. Twentekanaal"*, respectively, no or only one pharmaceutical compound could be detected.

The pharmaceuticals most frequently found were the anti-inflammatory drug diclofenac, the analgesics ibuprofen and phenazone, the lipid-lowering agents bezafibrate and clofibric acid, the antiepileptic carbamazepine, the betablockers metoprolol, atenolol, and sotalol, the iodinated x-ray contrast media iopamidol, iopromide, iomeprol, amidotrizoic acid, iohexol, and ioxitalamic acid, the antibiotics clarithromycin, roxithromycin, clindamycin, and sulfamethoxazole, as well as anhydro-erythromycin, the metabolite of the antibiotic erythromycin. Concentration levels were in the range of 10 ng/L to several hundred ng/L for samples from *"Bimmen", "WRK Ruw",* and *"WRK III Andijk"* and were below 25 ng/L for samples from *"Bethunepolder"* and *"Inn. Twentekanaal"*.

Table 1. Pharmaceuticals (and metabolites) under investigation

analgesics, antipyretics, antiphlogistics, antirheumatics:		
Diclofenac	Ibuprofen	Ketoprofen
Indometacine	Naproxen	Fenoprofen
Phenazone	dimethylaminophenazone	propyphenazone
lipid-lowering agents:		
clofibric acid	Bezafibrate	Gemfibrozil
Etofibrate	Fenofibrate	fenofibric acid
Simvastatin		
x-ray contrast media:		
Iopamidol	Iopromide	Iomeprol
amidotrizoic acid	Iodipamide	Iohexol
iopanoic acid	iotalamic acid	ioxaglic acid
ioxitalamic acid		
antiepileptic:		
Carbamazepine		
vasodilator:		
Pentoxifylline		
tranquilliser:		
Diazepam		
betablockers:		
Metoprolol	Propranolol	Atenolol
Bisoprolol	Sotalol	Pindolol
Betaxolol		
broncholytics, secretolytics:		
Salbutamol	Clenbuterol	Terbutaline
antineoplastic drugs:		
Cyclophosphamide	Ifosfamide	
antibiotics:		
Clarithromycin	Erythromycin	anhydro-erythromycin
Oleandomycin	Roxithromycin	Clindamycin
Spiramycin	Tylosin	Sulfadiazine
Sulfamerazine	Sulfamethoxazole	Sulfadimidine
Trimethoprim	Chloroamphenicol	Metronidazol
Ronidazol	Furazolidone	Dapsone
Virginiamycin	Amoxicillin	Ampicillin
penicillin G	penicillin V	Oxacillin
Nafcillin	Cloxacillin	Dicloxacillin
Ciprofloxacin	Enoxacin	Enrofloxacin
Norfloxacin	Ofloxacin	chlorotetracycline
Doxycycline	Meclocycline	oxytetracycline
Tetracycline		

Table 2 summarises the major results for the different sampling sites. The table gives the number of findings in all samples from the respective sites in 2002 and the concentration ranges found in the time period under investigation for those pharmaceutical compounds that could be detected in at least one sample.

Table 2. Pharmaceutical residues in Dutch waters: number of findings and concentration ranges (concentrations in ng/L)

	Bimmen *(12 samples)*	***WRK Ruw*** *(12 samples)*	***WRK III Andijk*** *(11 samples)*	***Inn. Twente-kanaal*** *(7 samples)*	***Bethune-polder*** *(3 samples)*
Diclofenac	12 (23-260)	10 (<10-310)	2 (<10-43)	-	-
Ibuprofen	5 (<10-41)	4 (<10-53)	-	1 (<10-12)	-
Indometacine	-	1 (<10-37)	-	-	-
Phenazone	6 (<10-67)	6 (<10-100)	2 (<10-15)	-	3 (21-44)
Propyphenazone	1 (<10-16)	2 (<10-18)	-	-	-
clofibric acid	10 (<10-31)	9 (<10-22)	5 (<10-23)	-	-
Bezafibrate	11 (<10-77)	11 (<10-190)	3 (<10-66)	-	-
Gemfibrozil	-	2 (<10-42)	2 (<10-22)	-	-
enofibric acid	2 (<10—18)	1 (<10-14)	-	-	-
Iopamidol	12 (100-410)	12 (88-470)	11 (17-120)	-	-
Iopromide	12 (100-370)	12 (160-730)	11 (55-180)	-	-
Iomeprol	12 (67-290)	12 (28-450)	11 (28-290)	-	-
amidotrizoic acid	12 (67-290)	12 (54-280)	11 (37-90)	-	-
Iohexol	12 (20-120)	12 (14-120)	10 (<10-54)	1 (<10-16)	-
ioxitalamic acid	12 (11-40)	12 (10-44)	7 (<10-20)	-	-
Carbamazepine	12 (100-410)	12 (47-500)	9 (41-260)	1 (<10-52)	-
Metoprolol	12 (18-54)	12 (11-42)	4 (<10-26)	1 (<10-22)	-
Atenolol	10 (<10-24)	7 (<10-23)	-	-	-
Sotalol	12 (48-110)	12 (56-140)	6 (<10-16)	1 (<10-31)	-
Clarithromycin	4 (<10-15)	5 (<10-14)	-	-	-
anhydro-erythromycin	12 (14-84)	12 (13-110)	8 (<10-39)	-	-
Roxithromycin	4 (<10-18)	5 (<10-15)	-	-	-
Clindamycin	5 (<10-17)	7 (<10-15)	-	-	-
Sulfamethoxazole	10 (<10-59)	12 10-53)	6 (<10-20)	-	-

It can be seen that for the sites *"Bimmen"* and *"WRK Ruw"* the situation is very similar. The same compounds were found and also the concentration ranges are comparable. Most important compounds for these two sites are diclofenac, clofibric acid, bezafibrate, carbamazepine, metoprolol, atenolol, sotalol, several iodinated x-ray contrast media, and sulfamethoxazole and anhydro-erythromycin. These pharmaceuticals were found in almost all samples un-der investigation. The highest concentrations of several hundreds of ng/L were found for carbamazepine and the iodinated X-ray contrast media. Looking at the temporal variations of the concentration levels in the samples from these two sites, no clear trend can be seen. For most of the pharmaceuticals only random variations of the concentrations in 2002 were observed.

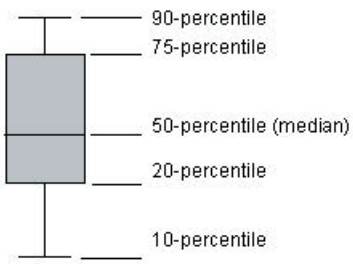
Remarkably, though, the carbamazepine values found by WRK in the routine screening at Nieuwegein tend to be generally somewhat higher and, incidentally, sudden pulses of this compound are detected *(De Bruin, personal communication, 2003*). This indicates sudden spills and may be related to the fact that carbamazepine is used also as an intermediate for other pharmaceuticals.

With the notable exception of iopromide no clear increases could be detected on the river section from the sampling site *"Bimmen/Lobith"* and *"WRK Ruw"*. This iopromide increase, however, is fairly prominent and indicates an input on that stretch of the river.

For the sampling site *"WRK III Andijk"* the same compounds were detected as was the case for *"Bimmen"* and "*WRK Ruw"*. The concentration levels, however, were significantly lower, due to dilution. Only for carbamazepine and for some X-ray contrast media concentrations above 100 ng/L were found, for all other compounds concentrations in samples from *"WRK III Andijk"* were below 100 ng/L.

Only in very few samples from the sampling site *"Inn. Twente-kanaal"* pharmaceuticals could be detected. In all samples from this site, concentration levels of the pharmaceuticals were close to the limit of detection (10 ng/L). For the sampling site *"Bethune-polder"* only one pharmaceutical, the analgesic phenazone, could be found. This compound was detected in all samples under investigation at concentration levels between 20 and 40 ng/L. Similar results have been obtained by Waterleidingbedrijf Amsterdam *(Smeenk, personal communication, 2003)* and have been attributed to bank infiltration from the Amsterdam Rhine canal and to waste deposits from a pharmaceutics producer. This pharmaceutical has been banned in the Netherlands in the early nineties. Nevertheless, this pharmaceutical was still detected in the Rhine sampling sites, indicating an ongoing input from upstream.

In the following diagrams the results for the most relevant pharmaceuticals, i.e. those pharmaceuticals which were found most often, are summarised for the different sampling sites using bar charts presenting the measured concentration levels. In addition, a statistical evaluation of the data has been performed for those compounds which were regularly found at at least one sampling site. The results of this evaluation are given as box-whisker plots whereby the following symbols are used:



• **Diclofenac**

*Figure 1: Concentration levels of **diclofenac***

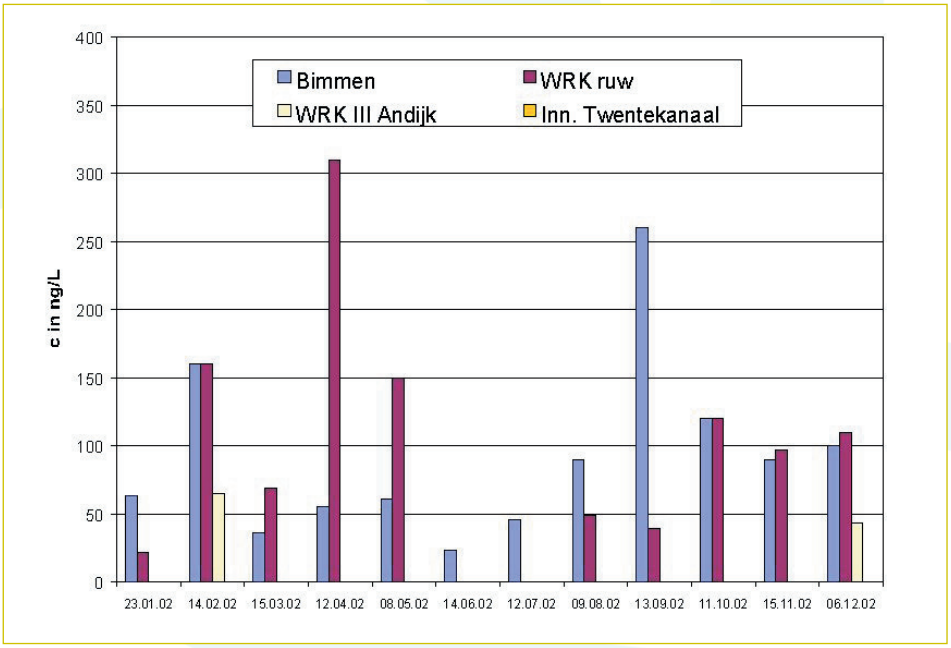
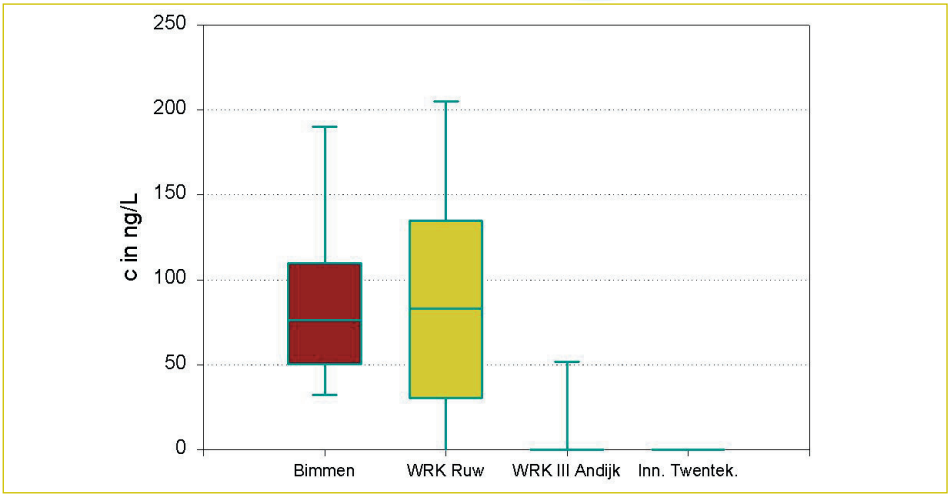
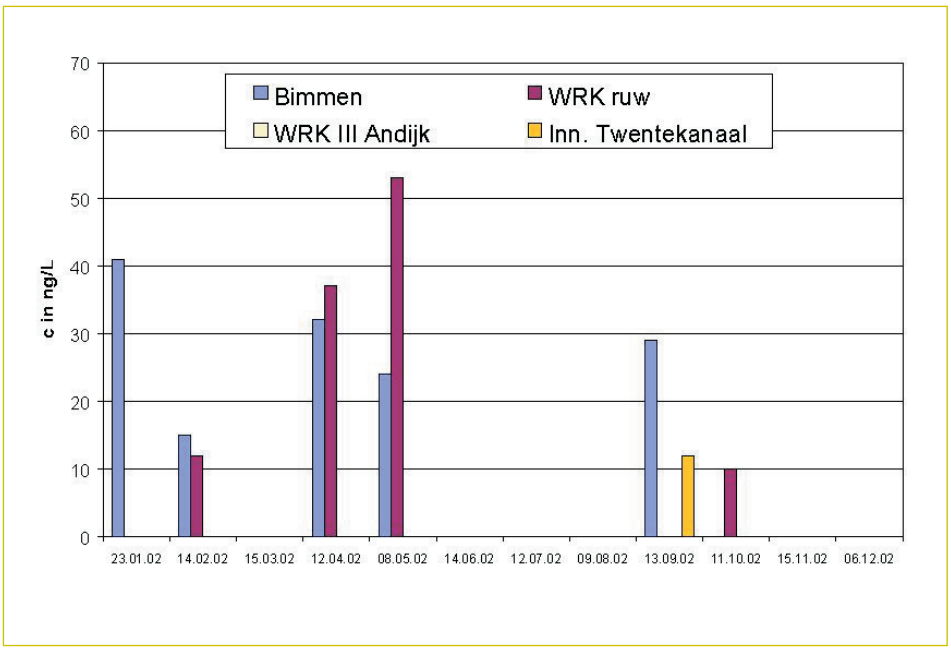


*Figure 2: Box-Whisker plot for **diclofenac***



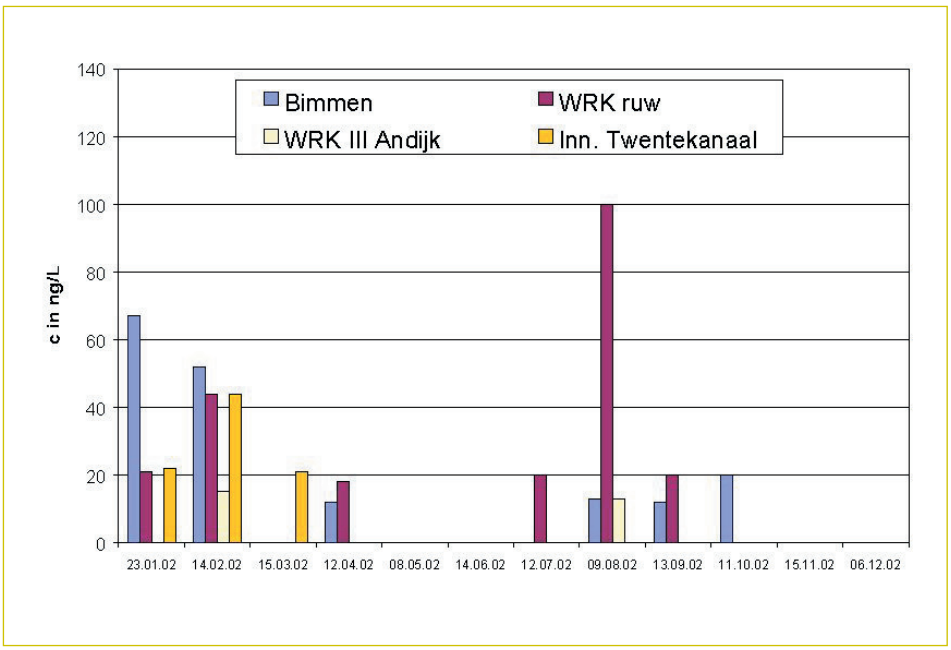
• **Ibuprofen**

*Figure 3: Concentration levels of **ibuprofen***



• **Phenazone**

*Figure 4: Concentration levels of **phenazone***



• **Clofibric acid**

*Figure 5: Concentration levels of **clofibric acid***

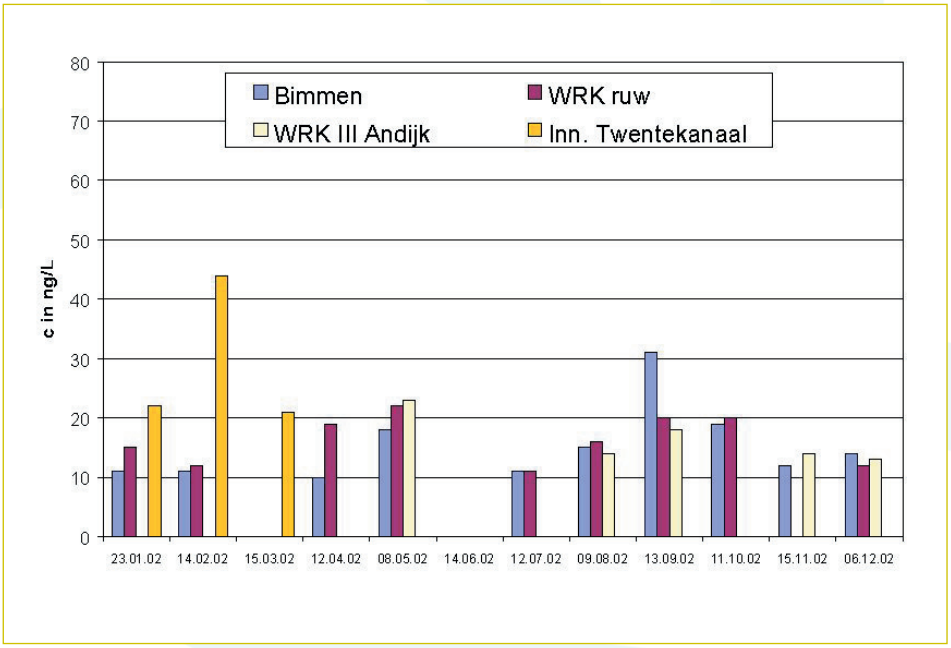
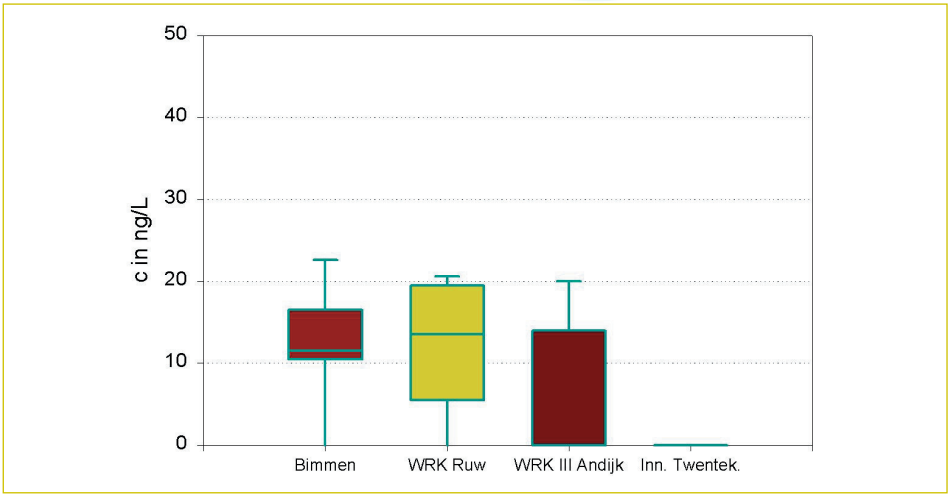


*Figure 6: Box-Whisker plot for **clofibric acid***



- **Bezafibrate**

*Figure 7: Concentration levels of **bezafibrate***

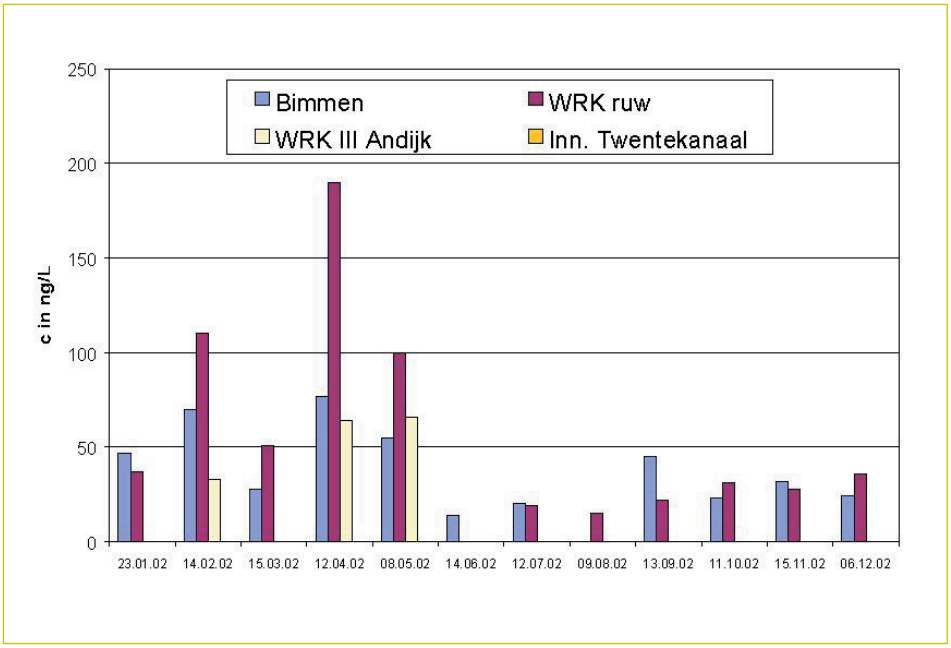
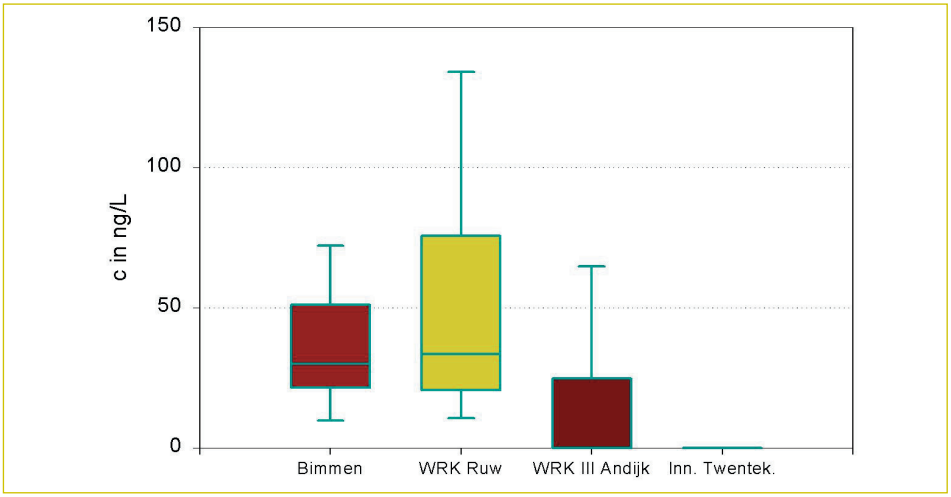


*Figure 8: Box-Whisker plot for **bezafibrate***



• **Carbamazepine**

*Figure 9: Concentration levels of **carbamazepine***

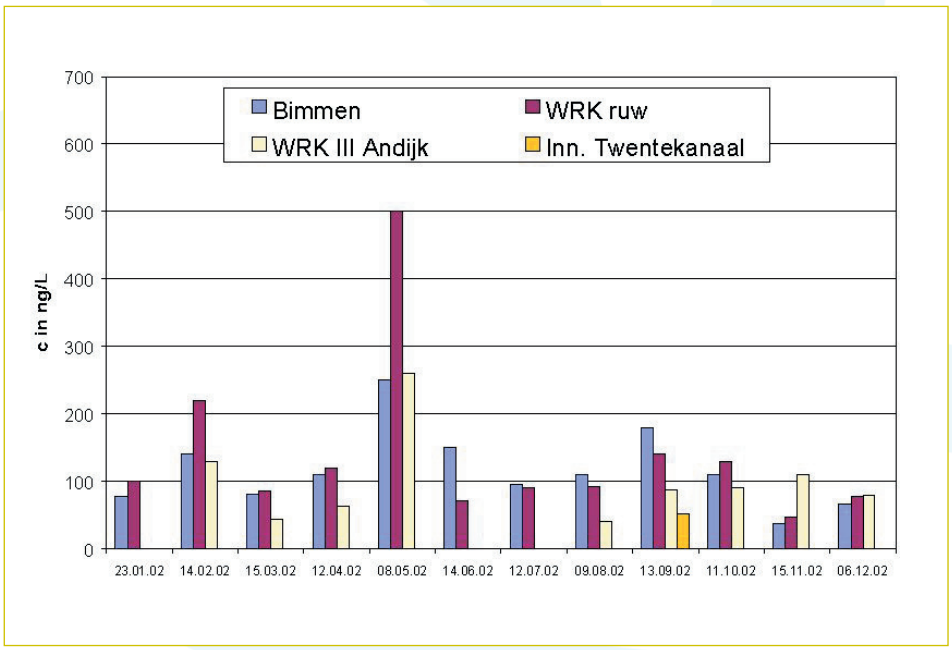
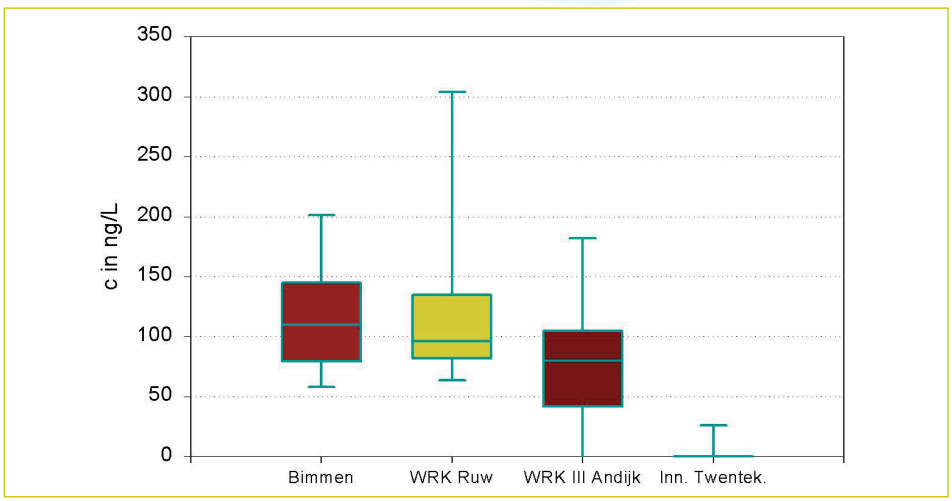


*Figure 10: Box-Whisker plot for **carbamazepine***



- **Iopamidol**

*Figure 11: Concentration levels of **iopamidol***

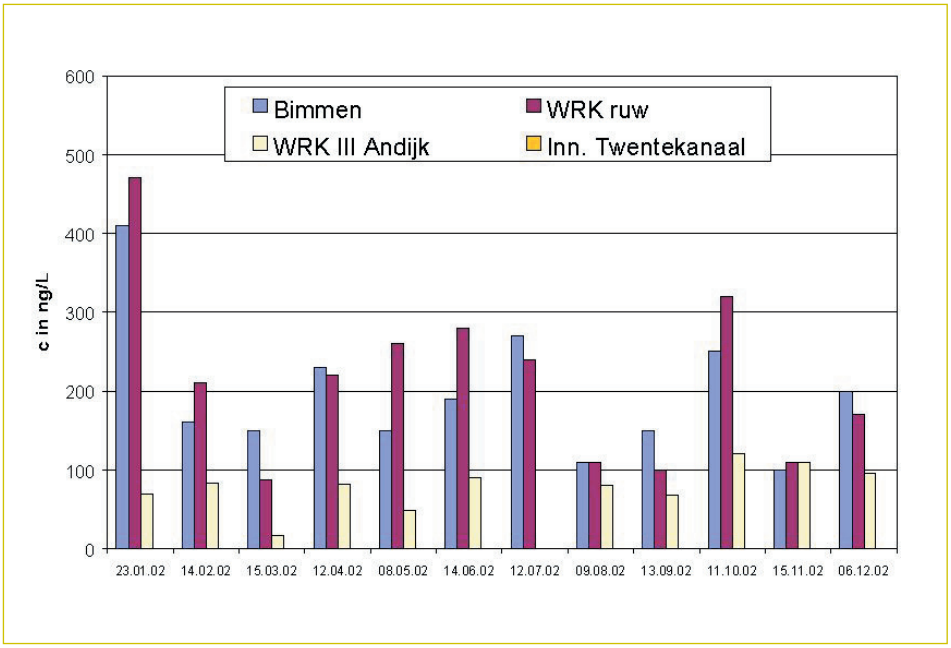
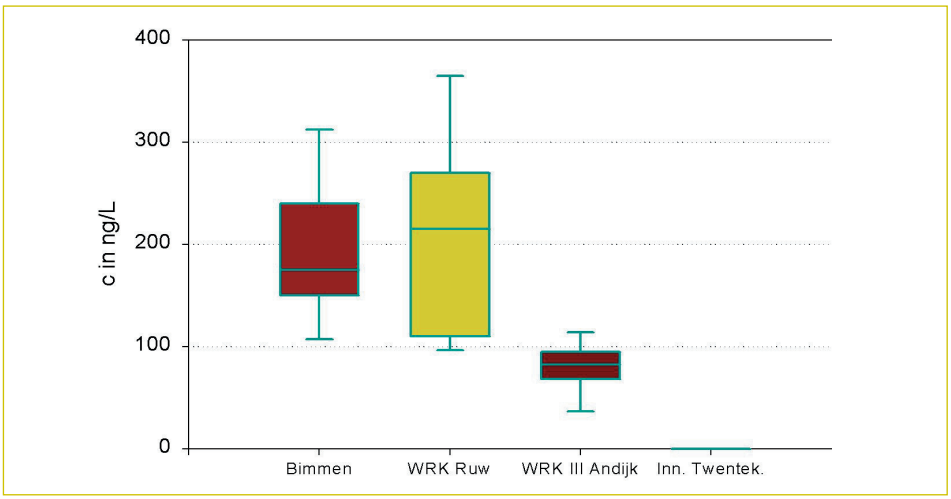


*Figure 12: Box-Whisker plot for **iopamidol***



• **Iopromide**

*Figure 13: Concentration levels of **iopromide***

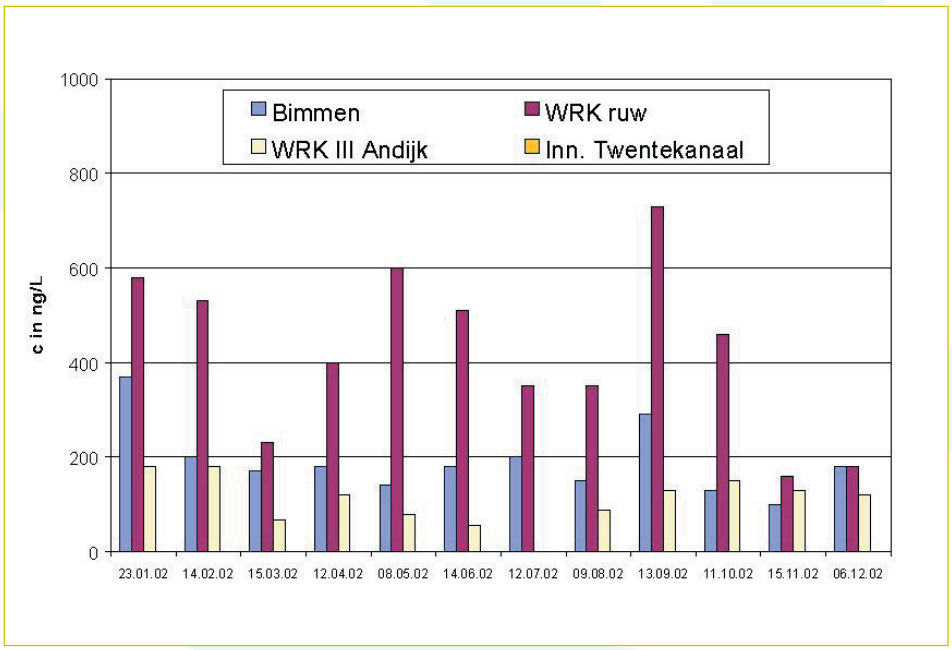
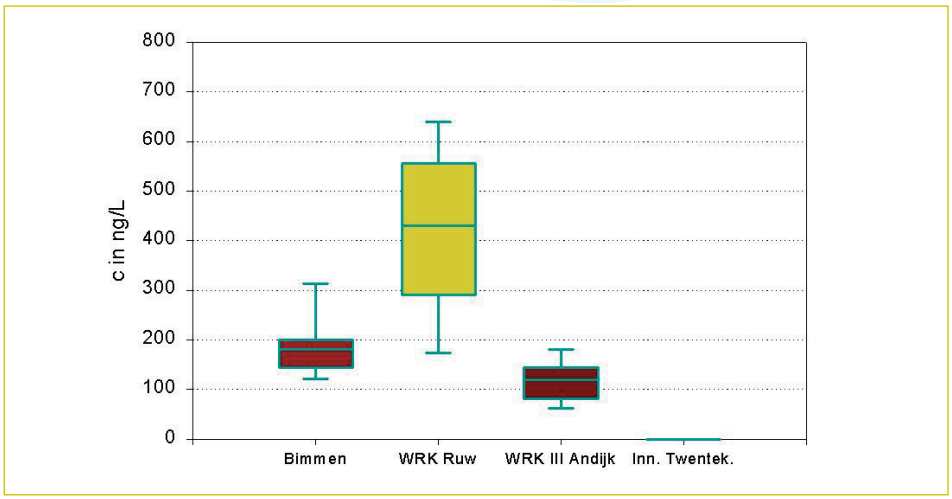


*Figure 14: Box-Whisker plot for **iopromide***



- **Iomeprol**

*Figure 15: Concentration levels of **iomeprol***

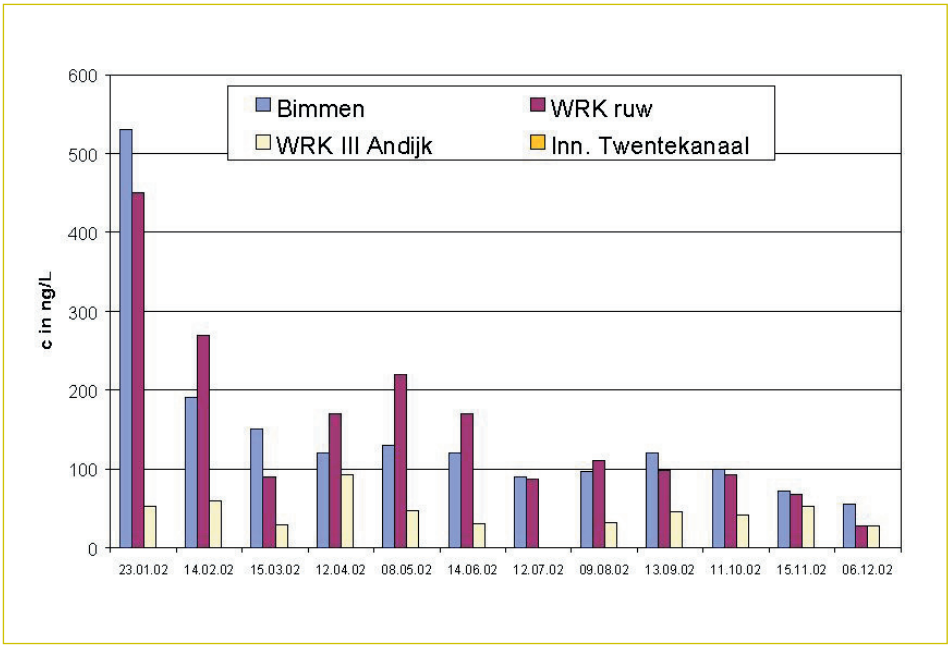
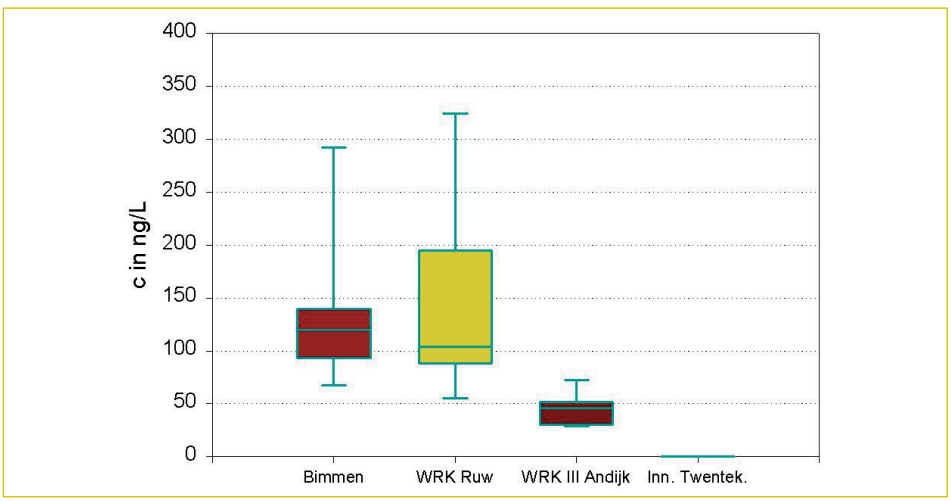


*Figure 16: Box-Whisker plot for **iomeprol***



• **Amidotrizoic acid**

*Figure 17: Concentration levels of **amidotrizoic acid***

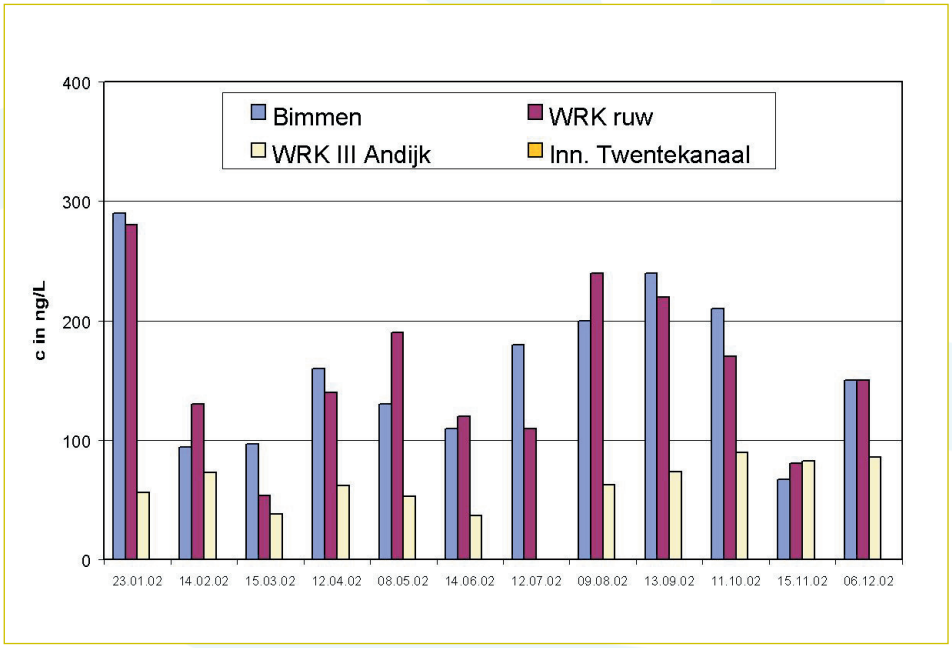
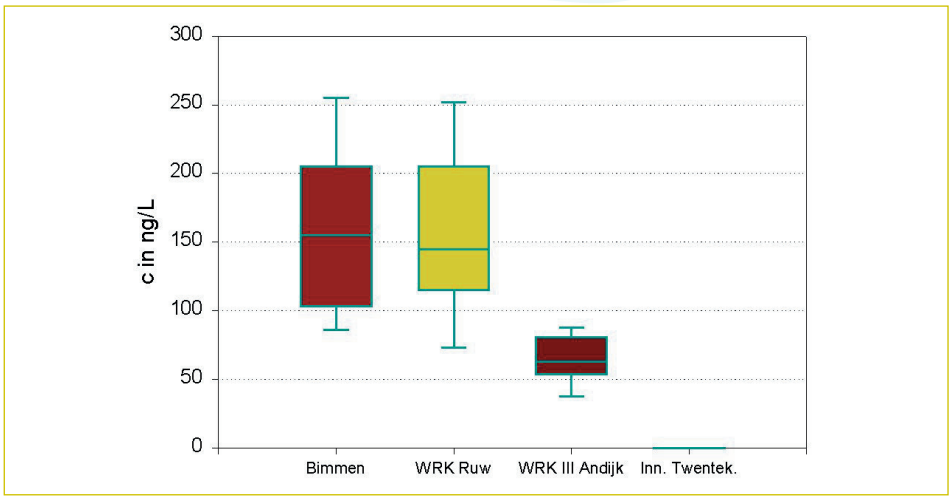


*Figure 18: Box-Whisker plot for **amidotrizoic acid***



- **Iohexol**

*Figure 19: Concentration levels of **iohexol***

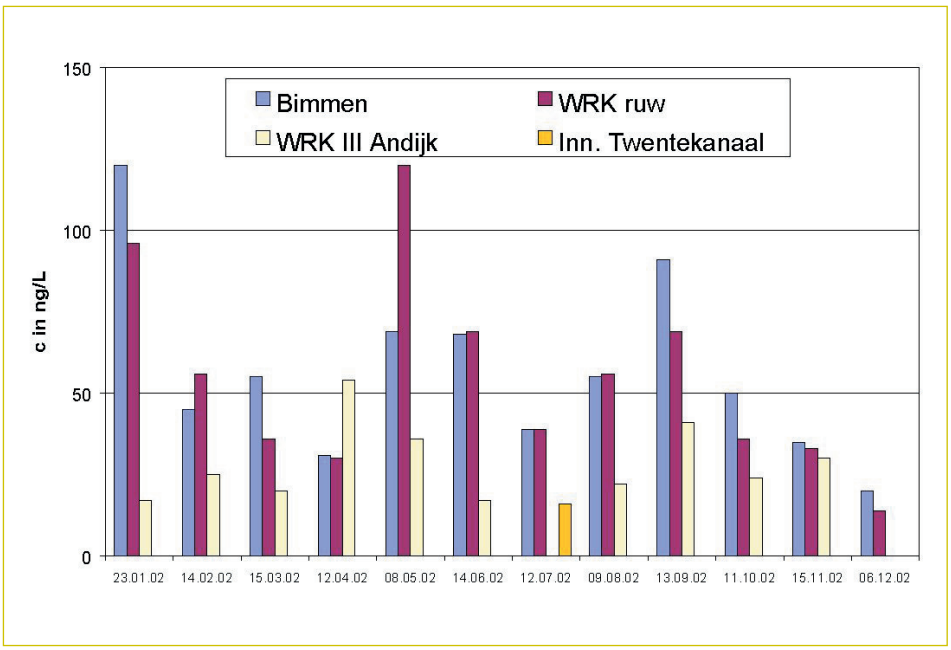
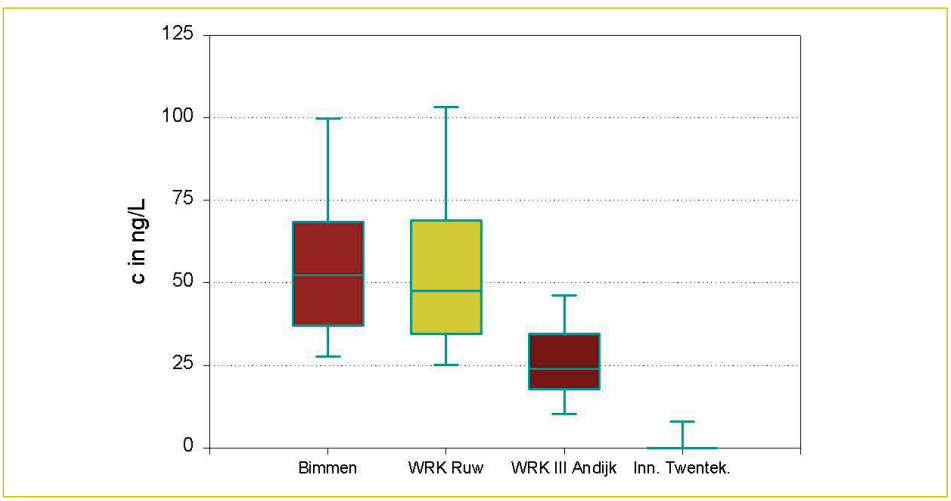
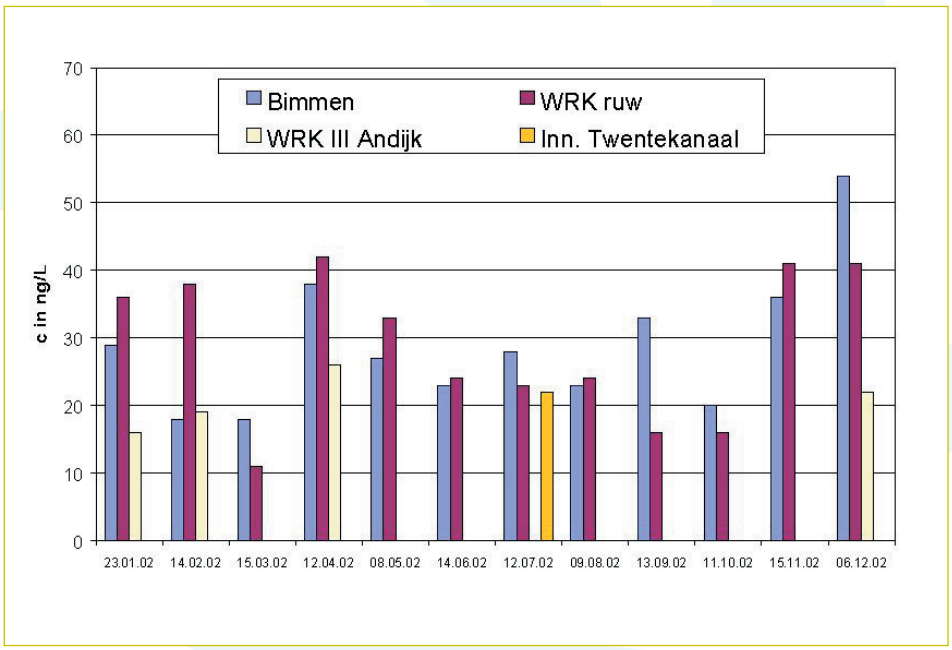


*Figure 20: Box-Whisker plot for **iohexol***



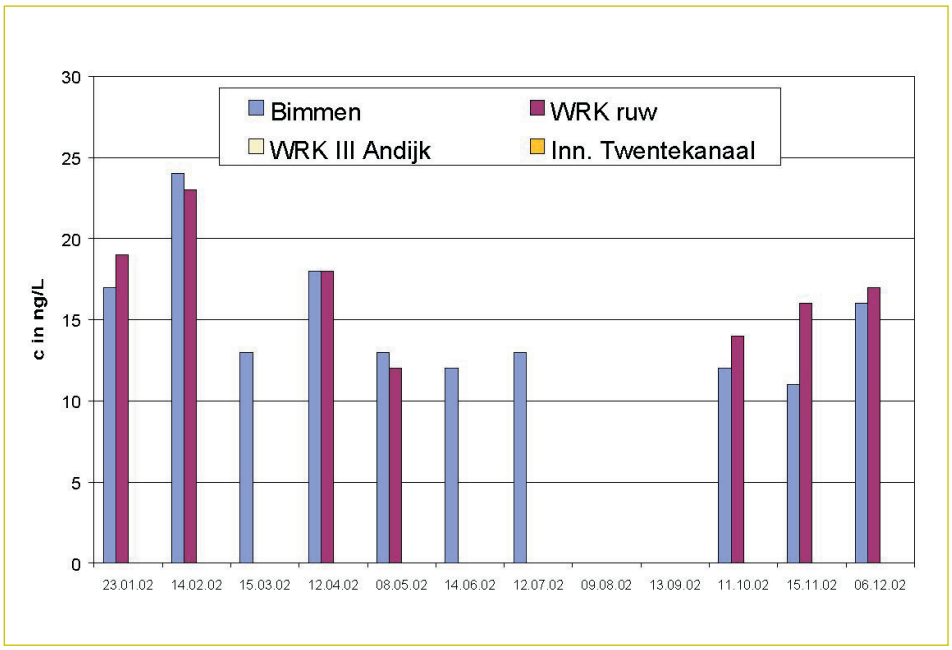
• **Metoprolol**

*Figure 21: Concentration levels of **metoprolol***



• **Atenolol**

*Figure 22: Concentration levels of **atenolol***



• **Sotalol**

*Figure 23: Concentration levels of **sotalol***

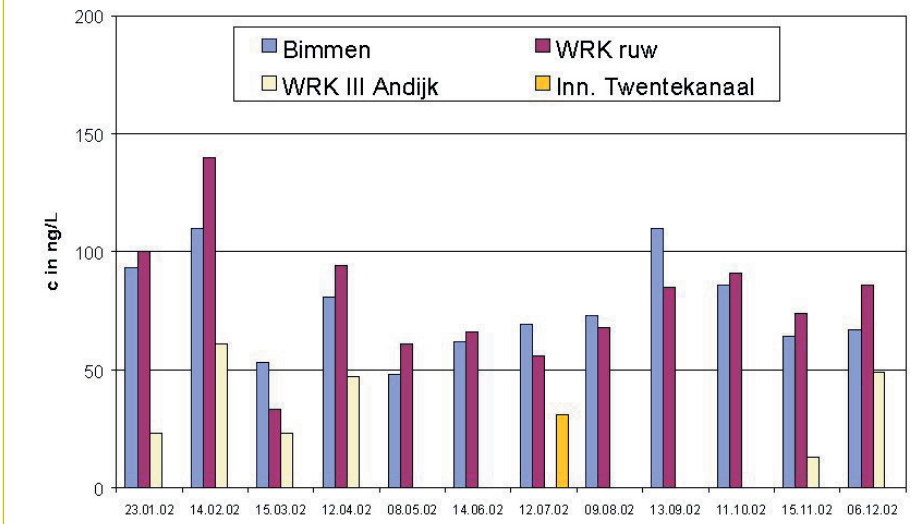
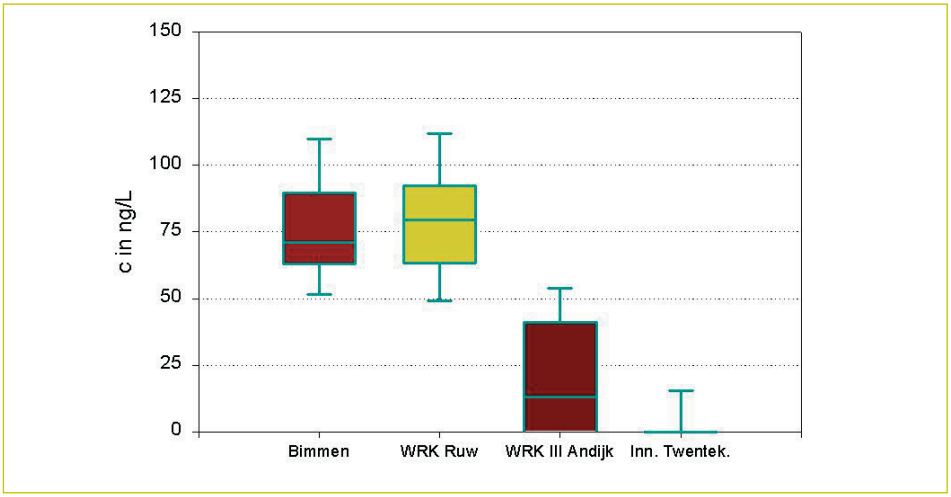


*Figure 24: Box-Whisker plot for **sotalol***



• **Anhydro-erythromycin**

*Figure 25: Concentration levels of **anhydro-erythromycin***

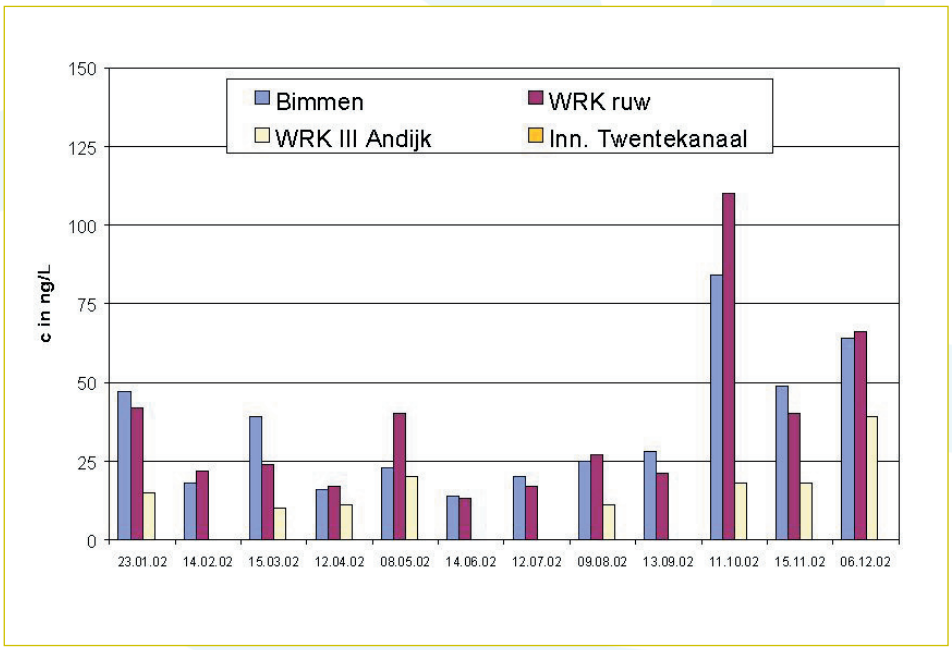
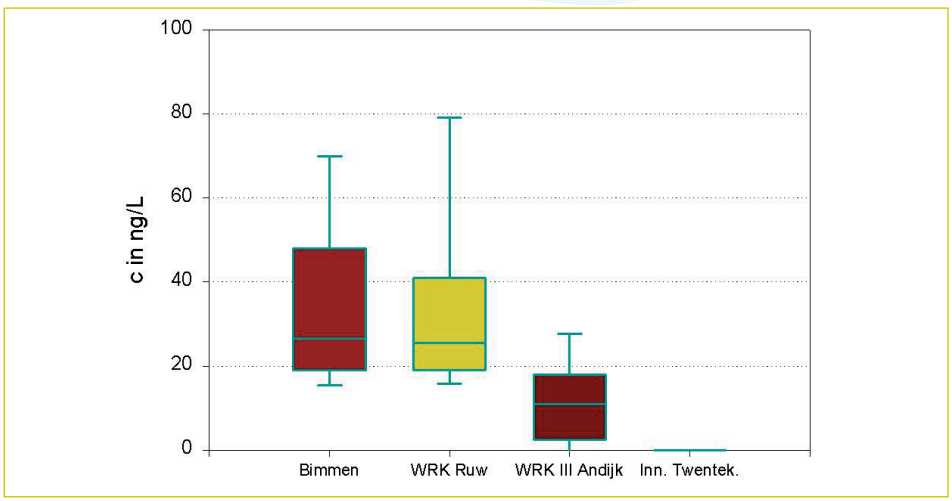


*Figure 26: Box-Whisker plot for **anhydro-erythromycin***



• **Sulfamethoxazole**

*Figure 27: Concentration levels of **sulfamethoxazole***

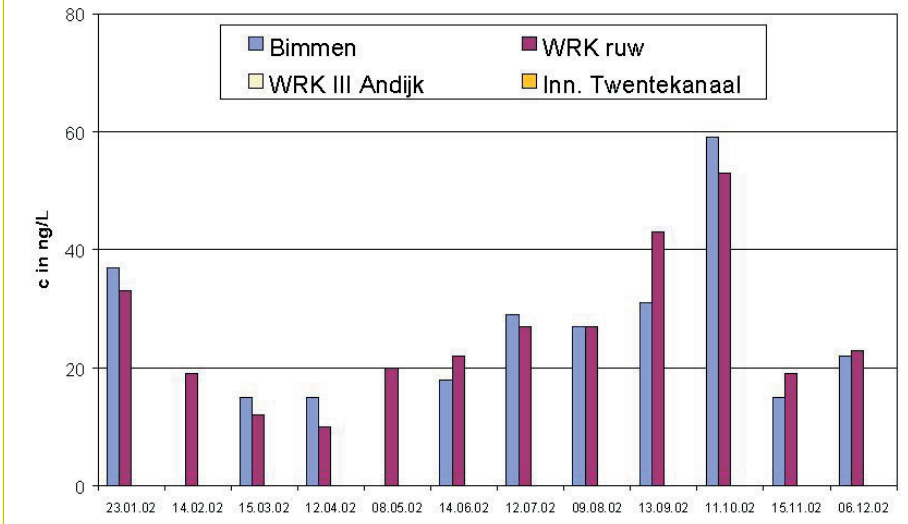
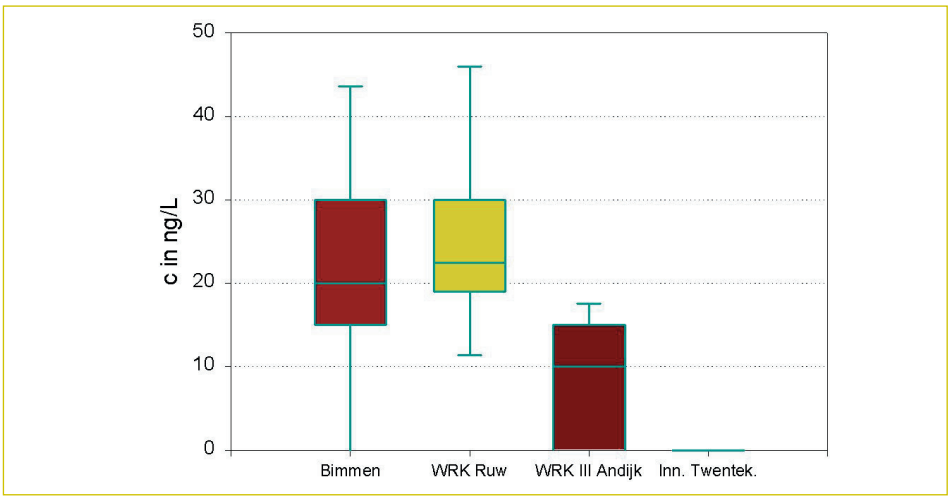


*Figure 28: Box-Whisker plot for **sulfamethoxazole***



Conclusions and Recommendations

Pharmaceuticals, as well as X-ray contrast media and antibiotics are shown to be present in the Dutch part of the Rhine catchment area. Concentration levels do not show a distinct seasonal pattern. The highest values are found at the German-Dutch border and at the intake point for drinking water 50 miles downstream, ranging up to several hundred nanograms per liter for certain compounds. For the other locations studied, the concentrations were distinctly lower. The pharmaceuticals most frequently found were the anti-inflammatory drug diclofenac, the analgesics ibuprofen and phenazone, the lipid-lowering agents bezafibrate and clofibric acid, the antiepileptic carbamazepine, the betablockers metoprolol, atenolol, and sotalol, the iodinated X-ray contrast media iopamidol, iopromide, iomeprol, amidotrizoic acid, iohexol, and ioxitalamic acid, the antibiotics clarithromycin, roxithromycin, clindamycin, and sulfamethoxazole, as well as anhydro-erythromycin, the metabolite of the antibiotic erythromycin.

The findings in this study are in agreement with the results of the research programs by RIZA, RIVM and Kiwa, conducted in parallel (see, for example www.riza.nl, report 2003.023). In view of the fact that the penetration of at least certain pharmaceuticals and, notably, certain XRF media through the treatment stages into the finished drinking water cannot be ruled out, it is recommended that these substances are incorporated in the routine monitoring programmes.

Like its international counterpart IAWR, the RIWA strives towards a source water quality that permits relatively simple, natural treatment processes to assure safe and healthy drinking water. Anthropogenic substances, and certainly such substances that cannot readily be removed by simple treatment, do not belong in surface water. An important source for these substances are effluents of wastewater treatment plants, as demonstrated in the RIZA study mentioned before. It is, therefore, recommended that water authorities investigate possibilities in order to minimize the inputs of such substances into the surface water.

Colofon

Authors:

Dr. Frank Sacher

DVGW-Technologiezentrum Wasser (TZW)
Karlsruher Strasse 84
76139 Karlsruhe
Germany
T: +49 (0)721 967 81 51
e-mail: sacher@tzw.de

Dr. Peter G. Stoks

RIWA
Groenendael 6
3439 LV Nieuwegein
Postbus 402
3430 AK Nieuwegein
The Netherlands
T: +31 (0)30 600 90 30
F: +31 (0)30 600 90 39
e-mail: riwa@riwa.org
web: www.riwa.org

Publisher: Vereniging van Rivierwaterbedrijven (RIWA)

Design: Meyson Communicatie, Amsterdam

Print: ATP Digitale Media, Zwanenburg

ISBN: 90-6683-106-5

November 2003