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OCCURRENCE OF DRUGS IN GERMAN SEWAGE TREATMENT PLANTS AND RIVERS*

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Abstract—The occurrence of 32 drug residues belonging to different medicinal classes like antiphlogistics, lipid regulators, psychiatric drugs, antiepileptic drugs, betablockers and β_2-sympathomimetics as well as five metabolites has been investigated in German municipal sewage treatment plant (STP) discharges, river and stream waters. Due to the incomplete removal of drug residues during passage through a STP, above 80% of the selected drugs were detectable in at least one municipal STP effluent with concentration levels up to 6.3 $\mu g\,l^{-1}$ (carbamazepine) and thus resulting in the contamination of the receiving waters. 20 different drugs and 4 corresponding metabolites were measured in river and stream waters. Mainly acidic drugs like the lipid regulators bezafibrate, gemfibrozil, the antiphlogistics diclofenac, ibuprofen, indometacine, naproxen, phenazone and the metabolites clofibric acid, fenofibric acid and salicylic acid as well as neutral or weak basic drugs like the betablockers metoprolol, propranolol and the antiepileptic drug carbamazepine were found to be ubiquitously present in the rivers and streams, mostly in the ng l^{-1}-range. However, maximum concentrations were determined up to 3.1 $\mu g\,l^{-1}$ and median values as high as 0.35 $\mu g\,l^{-1}$ (both bezafibrate). The drugs detected in the environment were predominantly applied in human medicine. It can therefore be assumed that the load of municipal STP effluents in the surface water highly influences the contamination. Due to their widespread presence in the aquatic environment many of these drugs have to be classified as relevant environmental chemicals.

Key words—drugs, antiphlogistics, lipid regulating agents, anticancer agents, diazepan, betablockers, β_2-sympathomimetics, carbamazepine, rivers and streams, sewage treatment plant effluents

INTRODUCTION

Organic compounds, isolated from plants as well as those synthesized by chemists, have been used as drugs for a long time. To date many tons of drugs are produced per year, and applied in human and veterinary medicine. Generally, exact production figures have not been published in the literature. However, the amounts of pharmaceuticals prescribed by physicians can be evaluated by multiplying the amount of daily dose with the number of prescribed daily doses per year. In Germany for instance up to about 100 t of individual drugs (Table 1) were prescribed in 1995 (Schwabe and Paffrath, 1995). This amount can increase dramatically when drugs are considered which can be purchased without prescription in the pharmacy. Due to this high application level, detectable concentrations of drugs and their metabolites may be expected in sewage. However, these concentrations are dependent on the drugs pharmacokinetical behavior (half life, urinary and faecal excretion, metabolism etc.).

Environmental exposure to drugs

Investigations in the United Kingdom as reported by Waggott (1981), Watts *et al.* (1983) and Richardson and Bowron (1985) revealed that drugs were present in the aquatic environment at concentrations up to approximately 1 $\mu g\,l^{-1}$, whereas the exact concentrations for the individual drugs were not always determined. Even in potable water and in ground water some drugs like diazepam, methaqualone and the antibiotics with penicilloyl groups have been determined. On Iona Island (Vancouver/Canada) the two antiphlogistics, ibuprofen and naproxen have been identified in sewage (Rogers *et al.*, 1986). Hignite and Azarnoff (1977) detected loads of salicylic acid up to 28.7 kg d^{-1} and of clofibric acid up to 2.9 kg d^{-1} in the effluents of the municipal sewage treatment plant (STP) of Kansas City (USA). In Germany the clofibric acid, a metabolite of three lipid regulating agents, has been identified in river and ground water and even in drinking water with concentration levels ranging up to 165 ng l^{-1} by Stan and Linkerhäger (1994), Heberer and Stan (1996). Our institute identified a

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Table 1. Estimated German prescription amounts from human application in 1995 and estimated human excretion rates of some selected drugs glucuronide-conjugates

	Pharmacokinetical excretion rate in %*		Estimated prescription amounts in 1995 in tons per year†
	Unchanged drug	Glucuronides‡	
Bezafibrate§	50	22	30
Clofibric acid (clofibrate, etofibrate, etophyllinclofibrate)	6	>90	16
Fenofibric acid (fenofibrate)	+	+ + +	15
Gemfibrozil¶	–	50	6
Diclofenac‖	15	< 1	75
Ibuprofen	1–8	14	105
Indometacine	10–20	80	6
Metoprolol	3–10	–	50
Propranolol	< 1	–	3
Carbamazepine**	1–2	+	80

+: small percentage, + + + : major percentage.
*Taken from literature (Forth *et al.*, 1996; Mutschler, 1996; Hardman *et al.*, 1996).
†Evaluated by using daily doses multiplied by the prescribed number of daily doses per year (Schwabe and Paffrath, 1996).
‡Conjugated only by phase II metabolism.
§Used literature: Abshagen *et al.*, 1979.
¶Used literature: Bendetta *et al.*, 1995; Todd and Ward, 1988.
‖Used literature: Landsdorp *et al.*, 1990.
**Used literature: Frey and Janz, 1985.

range of lipid regulating agents and antiphlogistics in STP effluents and river waters (Stumpf *et al.*, 1996a) as well as betablockers and β_2-sympathomimetics (Hirsch *et al.*, 1996). Even estrogens have been detected in the aquatic environment by several authors in the ng l^{-1}-range (Tabak and Bunch, 1970; Rurainski *et al.*, 1977; Tabak *et al.*, 1981; Aherne and Briggs, 1989; Shore *et al.*, 1993; Stumpf *et al.*, 1996b).

However, there is still a lack of information about the behavior of drugs during their passage through a STP and about the contamination of the aquatic environment due to the multitude of drugs applied in medicine. For instance in Germany about 2900 different drugs are allowed to be used in human medicine (Rote Liste, 1994). The aim of this work was to survey the exposure of German STP effluents and German rivers to drugs and some selected metabolites.

EXPERIMENTAL SECTION

Methods

Several methods have been used for the determination of drugs and their metabolites belonging to distinct medicinal groups (see appendix) in the lower ng l^{-1}-range including solid phase extraction, derivatization, detection and confirmation by GC/MS and GC/MS/MS or LC-electrospray/MS/MS. The methods have already been published or submitted and are therefore only briefly mentioned (Stumpf *et al.*, 1996a; Hirsch *et al.*, 1996; Ternes *et al.*, 1998a; Ternes *et al.*, 1998b).

Firstly, a multi-method has been developed which allows the determination of betablockers and β_2-sympathomimetics as well as neutral drugs like diazepam or carbamazepine at concentrations in the ng l^{-1}-range after a joint solid phase extraction (Ternes *et al.*, 1998a). For the detection of betablockers, β_2-sympathomimetics by GC/MS a two step derivatization with silylation and acetylation has been developed, whereas all other neutral drugs can be measured without any derivatization. Alternatively, a time-saving method has been developed using detection by LC-electrospray/MS/MS, in order to determine neutral drugs (e.g. carbamazepine, phenazone, ifosfamide and cyclophosphamide) down to 10 ng l^{-1} in river water as well as in STP effluents (Ternes *et al.*, 1998a). The LC/MS/MS method was used for sewage, STP effluents and highly organic polluted river and stream water samples. Secondly, a multi-method allows the determination of acidic drugs having a carboxylic moiety and additionally in some cases one or two hydroxy groups down to lower ng l^{-1}-range (Ternes *et al.*, 1998b). Lipid regulating agents, antiphlogistics and three metabolites with carboxylic and hydroxy groups are included within this method. A separate determination of the acidic drugs is also performable (Stumpf *et al.*, 1996a) as for the metabolites. The acidic drugs and the five metabolites were quantified and confirmed by GC/MS or GC/MS/MS after solid phase extraction and methylation by diazomethane. All analysis of environmental samples have been carried out by utilizing at least 5 point calibrations over the whole procedure of the previously described methods.

Table 2. Flow rates of a municipal sewage treatment plant near Frankfurt/Main at different sampling periods

	24.5–30.5.96	24.6–30.6.96	28.1–2.2.97	24.3–30.3.97	23.11–30.11.97
Average flow rate (m^3 d^{-1})	64,720 ± 12,500	54,300 ± 6,430	55,320 ± 1,600	63,190 ± 10,880	53,300 ± 6,200
Investigated drugs	lipid regulating agents, antiphlogistics	betablockers, β_2-sympathomimetics	lipid regulating agents, antiphlogistics	neutral drugs, ASA-metabolites	neutral drugs

Sampling procedure

Sampling of corresponding influents and effluents of a STP. In five sampling periods (24.5–30.5.96, 24.6–30.6.96, 28.1–2.2.97, 24.3–30.3.97 and 23.11–30.11.97) composite samples from a German municipal STP were taken daily from the raw influent and the corresponding final effluent over a period of 6 d. Sampling was carried out by a flow proportional automatic sampler, whereby the composite samples of the final effluent were taken time related to the influent. The municipal STP near Frankfurt/Main is connected to about 312,000 population equivalents. It consists of three commonly used main treatment steps: preliminary clarification followed by an aerator tank with the addition of Fe(II)chloride for phosphate elimination and finally end point clarification. The average flow rates at the sampling dates are listed in Table 2. All cooled water samples were analyzed within two days in order to keep microbial degradation to a minimum.

Sampling of STP effluents and rivers. Effluents of up to 49 municipal STP, treating mainly household discharges, were sampled in order to analyze drug residues. All STP consisted of three commonly used main treatment steps: preliminary and final clarification and an aerator tank. Additionally, 43 STP treatment plants are equipped with phosphate elimination, 25 STP with a nitrification and 13 with a denitrification treatment step. In general, random samples of the STP effluents were taken. The sampling periods for the determination of acidic drugs like lipid regulating agents and some antiphlogistics from STP effluents, rivers and streams were from November 1995 to June 1996 and for the analysis of betablockers and β_2-sympathomimetics from April 1996 to December 1996. Neutral drugs like carbamazepine, phenazone or diazepam and the metabolites of acetylsalicylic acid were screened in STP effluents as well as in rivers and streams from October 1996 to November 1997.

Daily composite samples were taken from the rivers Lahn (Oberbiel), Kinzig (Hanau), Fulda (Wahnhausen), Werra (Heldra), Main (Bischofsheim), Rhine (Mainz), Nidda (Nied) as well as from the stream Schwarzbach (Trebur). Additionally, random samples were taken from the Ruhr (Essen), Mosel (Wehlen), Neckar (Heidelberg), Elbe (Hamburg) and from 24 small rivers and streams mostly located in the Hessian Ried area (center of Germany). From the river Rhine also daily composite samples were taken over a 14 d sampling period (from January 1996 to June 1996 and September 1996 to December 1996) at three locations situated at the Theodor Heuss bridge connecting Mainz and Wiesbaden. Additionally, in December 1996 random samples were taken from the river Main at different distances between km 77 and km 4.5 from its entry point into the river Rhine.

RESULTS AND DISCUSSION

Elimination of drugs after passage through a municipal STP

The removal of drug residues during passage through a municipal STP near Frankfurt/Main was investigated by the analysis of corresponding daily composite water samples of the raw influent and final effluent after filtration (0.45 μm) at different periods.

Average loads up to 3.0 kg d^{-1} (salicylic acid) were determined in the influent and up to 114 g d^{-1} (carbamazepine) in the final effluent. In Fig. 1 all detected drugs are illustrated, which were mainly present in the STP discharge. The elimination rates

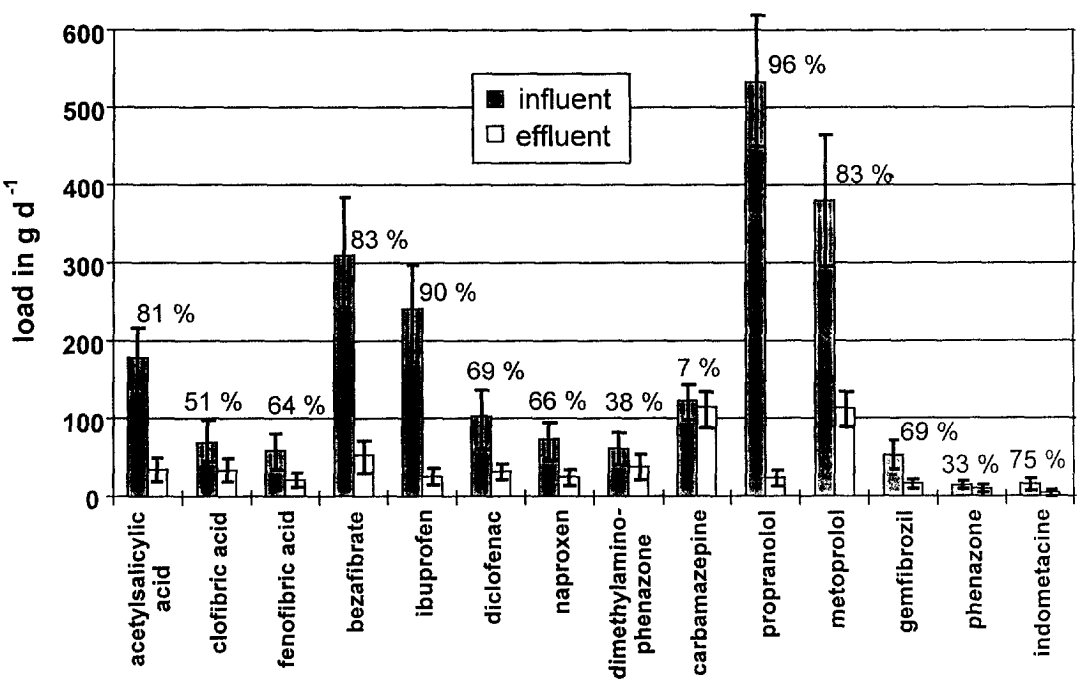

Fig. 1. Elimination of different drugs during passage through a municipal sewage treatment plant located near Frankfurt/Main over 6 d. Sampling periods, betablockers, β_2-sympathomimetics 24.6.–30.6.97; antiphlogistics, lipid regulating agents: 28.1.–2.2.97; 24.5.–30.5.96; remaining drugs: 24.3.–29.3.97; 23.11.–30.11.97.

of the investigated drugs during passage through the STP ranged from 7% (carbamazepine) to greater than 99% (salicylic acid). Generally more than 60% of the drug residues detected in the influent were removed. Only carbamazepine, clofibric acid, phenazone and dimethylaminophenazone showed lower average removal rates. Fenofibrate, acetaminophen and the metabolites of acetylsalicylic acid (salicylic acid, *o*-hydroxyhippuric acid, gentisic acid) were not detectable in the discharge of the STP, although sometimes extremely high concentrations up to 54 $\mu g\ l^{-1}$ (salicylic acid) were determined in the influent. Hence, these drugs and metabolites were efficiently removed by the selected municipal STP. It should be noted that the observed elimination rates of drug residues during passage through the STP could not be differentiated in effects of sorption and biodegradation, since the drugs sorption behavior on activated sludge was not investigated. However, most of the drugs examined in this study were incompletely eliminated and thus contaminate the receiving water.

The removal rates of several antiphlogistics and lipid regulating agents was investigated during a another sampling period (24.5.–30.5.96, Table 2), which included a rainfall event on the fourth day and led to an elevated flow rate of about 50%, from average 59,500 $m^3\ d^{-1}$ to 89,900 $m^3\ d^{-1}$ (Fig. 2). As shown in Fig. 2 the elimination rates of some drugs like bezafibrate, diclofenac, naproxen and clofibric acid were significantly reduced on the rainfall day and did not recovered until the sixth day, with the exception being bezafibrate. For bezafibrate a reduced elimination rate (< 5%) was observed even at the sixth day, the last day of the investigation period. These results indicate that the rainfall event may have been presumably responsible for the decreased drug elimination rates by the STP. Whether these effects were caused by a reduced microbial activity or by altered sorption and flocculation conditions within this rain period or both, cannot be deduced. Presumably, the treatment in the aerator tank with the simultaneously performed flocculation was mainly responsible for the observed drug removal rates. However, to prove this hypothesis further comparable investigations concerning the sorption and biodegradation behavior of drugs within the commonly utilized treatment steps in municipal STP at different seasons are essential to reveal the efficiency of single treatment processes.

Screening of drug levels in sewage plant effluents as well as rivers and streams

Due to the incomplete elimination of many pharmaceutical compounds and metabolites (e.g. clofibric acid and fenofibric acid) in the selected municipal STP near Frankfurt/Main a screening

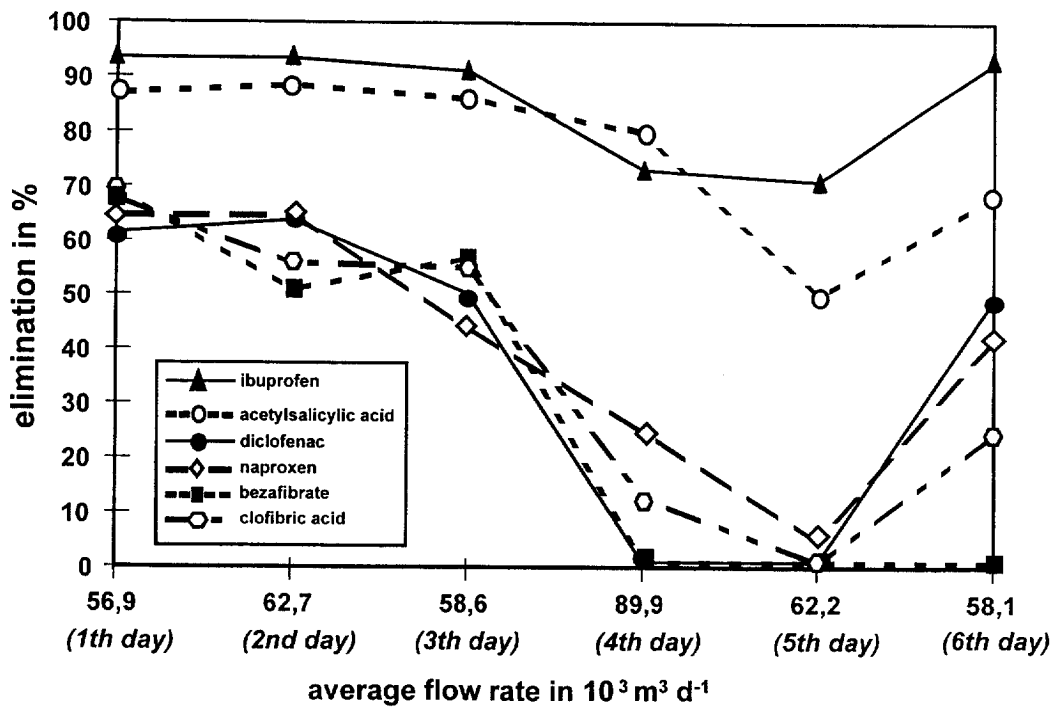

Fig. 2. Elimination of drugs during passage through a municipal sewage treatment plant near Frankfurt/Main over 6 d including a rainfall event: Sampling period, influents: May 24th to May 29th 1996, effluents: May 25th to May 30th 1996.

Table 3. Concentrations of lipid regulators and metabolites in STP effluents as well as rivers and streams

Substances in $\mu g\ l^{-1}$	STP effluents						Rivers and streams					
	LOD*	Number STP	$n > LOD^*$	Median $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$	LOD*	Samples/rivers	$n > LOD^*$	Median $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$
Lipid regulating agents												
Bezafibrate	0.25	49	48	2.2	3.4	4.6	0.025	43/22	39	0.35	1.2	3.1
Gemfibrozil	0.050	49	39	0.40	0.84	1.5	0.010	43/22	28	0.052	0.19	0.51
Fenofibrate	0.050	20	2	n.d.	n.d.	0.03	0.010	36/22	0	n.d.	n.d.	n.d.
Etofibrate	0.10	20	0	n.d.	n.d.	n.d.	0.030	36/22	0	n.d.	n.d.	n.d.
Clofibrate	0.10	20	0	n.d.	n.d.	n.d.	0.030	36/22	0	n.d.	n.d.	n.d.
Metabolites												
Clofibric acid	0.050	49	47	0.36	0.72	1.6	0.010	43/22	35	0.066	0.21	0.55
Fenofibric acid	0.050	49	41	0.38	0.68	1.2	0.010	43/22	26	0.045	0.17	0.28

*Limit of detection, n.d.: not detectable.

Table 4. Concentrations of antiphlogistics in STP effluents as well as rivers and streams

Substances $\mu g\ l^{-1}$	STP effluents						Rivers and streams					
	LOD*	Number STP	$n > LOD^*$	Median in $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$	LOD*1	Samples/rivers	$n > LOD^*$	Median in $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$
Antiphlogistics												
Diclofenac	0.050	49	49	0.81	1.6	2.1	0.010	43/22	43	0.15	0.80	1.20
Ibuprofen	0.050	49	42	0.37	1.2	3.4	0.010	43/22	35	0.07	0.28	0.53
Indometacine	0.050	49	49	0.27	0.40	0.60	0.010	43/22	35	0.04	0.17	0.20
Naproxen	0.050	10	10	0.30	0.42	0.52	0.010	20/20	20	0.070	0.15	0.39
Fenoprofen	0.050	49	0	n.d.	n.d.	n.d.	0.010	43/22	0	n.d.	n.d.	n.d.
Ketoprofen	0.050	49	37	0.20	0.25	0.38	0.010	43/22	5	n.d.	0.12	0.12
Phenazone	0.10	30	28	0.16	0.30	0.41	0.020	26/20	21	0.024	0.15	0.95
Acetaminophen	0.50	49	4	n.d.	n.d.	6.0	0.150	31/16	0	n.d.	n.d.	n.d.
Acetylsalicylic acid	0.10	49	22	0.22	0.32	1.5	0.020	43/22	17	n.d.	0.16	0.34
Dimethylaminophenazone	0.10	16	3	n.d.	0.15	1.0	0.030	26/20	2	n.d.	n.d.	0.34
Meclofenamic acid	0.050	10	0	n.d.	n.d.	n.d.	0.010	43/22	0	n.d.	n.d.	n.d.
Tolfenamic acid	0.050	10	0	n.d.	n.d.	n.d.	0.010	30/20	0	n.d.	n.d.	n.d.
Metabolites												
Salicylic acid	0.050	36	9	n.d.	0.063	0.14	0.010	35/19	24	0.025	0.13	4.1
o-hydroxyhippuric acid	0.20	36	0	n.d.	n.d.	n.d.	0.075	35/19	0	n.d.	n.d.	n.d.
Gentisic acid	0.20	36	3	n.d.	0.20	0.59	0.075	35/19	5	n.d.	0.11	1.2

*Limit of detection, n.d.: not detectable.

Table 5. Concentrations of betablockers, β_2-sympathomimetics in STP effluents as well as rivers and streams

	STP effluents						Rivers and streams					
Substances $\mu g\ l^{-1}$	LOD*	Number STP	$n >$ LOD*	Median in $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$	LOD*	Samples/rivers	$n >$ LOD*	Median in $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$
						Betablockers						
Metoprolol	0.025	29	29	0.73	1.3	2.2	0.010	45/23	38	0.045	1.2	2.2
Propranolol	0.025	29	28	0.17	0.23	0.29	0.010	45/23	26	0.012	0.44	0.59
Nadolol	0.025	29	20	0.025	0.042	0.06	0.010	45/23	0	n.d.	n.d.	n.d.
Carazolol	0.025	29	13	n.d.	0.070	0.12	0.010	45/23	3	n.d.	0.10	0.11
Timolol	0.025	29	2	n.d.	n.d.	0.07	0.010	45/23	1	n.d.	n.d.	0.01
Betaxolol	0.025	29	17	0.057	0.10	0.19	0.010	45/23	1	n.d.	n.d.	0.028
Bisoprolol	0.025	29	17	0.057	0.13	0.37	0.010	45/23	19	n.d.	0.19	2.9
						β_2-sympathomimetics						
Fenoterol	0.050	29	1	n.d.	n.d.	0.060	0.010	45/23	1	n.d.	n.d.	0.061
Terbutalin	0.050	29	11	n.d.	0.087	0.12	0.010	45/23	0	n.d.	n.d.	n.d.
Salbutamol	0.050	29	10	n.d.	0.072	0.17	0.010	45/23	2	n.d.	n.d.	0.035
Clenbuterol	0.050	29	5	n.d.	n.d.	0.08	0.010	45/23	2	n.d.	n.d.	0.050

*Limit of detection, n.d.: not detectable.

Table 6. Concentrations of diazepam, carbamazepine and anticancer agents in STP effluents as well as rivers and streams

	STP effluents						Rivers and streams					
Substances $\mu g\ l^{-1}$	LOD*	Number STP	$n >$ LOD*	Median in $\mu g\ l^{-1}$	90-percentile	Maximum $\mu g\ l^{-1}$	LOD*	Samples/ rivers	$n >$ LOD*	Median in $\mu g\ l^{-1}$	90-percentile	maximum $\mu g\ l^{-1}$
						Psychiatric drugs						
Diazepam	0.030	20	8	n.d.	0.03	0.04	0.030	30/20	0	n.d.	n.d.	n.d.
						Antiepileptic drugs						
Carbamazepine	0.050	30	30	2.1	3.7	6.3	0.030	26/20	24	0.25	0.82	1.1
						Cytostatic agents						
Ifosfamide	0.010	16	2	n.d.	0.040	2.9	0.010	26/20	0	n.d.	n.d.	n.d.
Cyclophosphamide	0.010	16	4	n.d.	0.018	0.020	0.010	26/20	0	n.d.	n.d.	n.d.

*Limit of detection, n.d.: not detectable.

program of up to 49 different German municipal STP effluents has been conducted. Finally, German rivers and streams were screened in order to assess the occurrence of drug residues. The analytical data are listed in Tables 3–6.

Lipid regulating agents. The lipid regulators bezafibrate and gemfibrozil were present in the majority of German municipal STP effluents investigated in this study (Table 3). For bezafibrate concentrations up to 4.6 $\mu g\,l^{-1}$ and median values surprisingly as high as 2.2 $\mu g\,l^{-1}$ have been observed. Rivers and streams were also polluted by these drugs, however median concentrations declined by a factor between 5 and 10, as compared to STP discharges.

The unpolar lipid regulators (clofibrate, etofibrate and fenofibrate) were in general not detectable in STP effluents, but their polar metabolites clofibric acid and fenofibric acid were present with concentration levels up to 1.6 $\mu g\,l^{-1}$ and 1.2 $\mu g\,l^{-1}$ respectively. Concentration levels within the ng l^{-1}-range were observed for the above two metabolites in rivers and streams. These two examples illustrate the importance of the principal metabolites for the contamination of the aquatic environment, due to their frequently increased polarity. Clofibric acid is the active metabolite of the lipid regulators clofibrate, etofyllinclofibrate and etofibrate, whereas fenofibric acid is only derived from fenofibrate (Balfour *et al.*, 1990; Forth *et al.*, 1996; Mutschler, 1996). The complete hydrolysis of the original drugs to fenofibric acid and clofibric acid occurs immediately after intake. Their principal excretion products are glucuronides of the acidic metabolites, which are formed by conjugation of the carboxylic moiety with glucuronic acid. The percentage of the glucuronides excreted exceeded mostly 60% (Table 1), whereas the portion of the non-conjugated acids are generally very small (below 10%). Original non-hydrolyzed drugs are not excreted, but other metabolites like reduced fenofibric acid (Balfour *et al.*, 1990) are present in urine or faeces in small amounts as glucuronide or unmetabolized. Because the concentration levels of clofibric acid and fenofibric acid were as high as 1.6 $\mu g\,l^{-1}$ in STP effluents, it appears most likely that their glucuronide-conjugates were at least partially cleaved in sewage or during passage through a municipal STP and thus increase the relevant environmental concentrations.

Antiphlogistics. 6 of the 12 selected antiphlogistics (analgesic-antipyretic and antiinflammatory agents) were detected in more than 50% of the investigated municipal STP effluents as listed in Table 4. Mainly diclofenac, ibuprofen, indometacine, naproxen, ketoprofen and phenazone were present in the STP discharges. The 90-percentile concentrations of diclofenac and ibuprofen exceeded 1 $\mu g\,l^{-1}$. With the exception of ketoprofen these drugs were also detected in rivers and streams, with diclofenac having the highest concentrations. The median concentration for diclofenac was 0.81 $\mu g\,l^{-1}$ in STP effluents and 0.15 $\mu g\,l^{-1}$ in river and stream waters, whereas the median values of the other antiphlogistics were lower by at least a factor of two. The antiphlogistics, present in the rivers and STP effluents, were mainly applied in human medicine (Mutschler, 1996; Forth *et al.*, 1996). Only naproxen is additionally used in veterinary medicine with appreciable amounts (Löscher *et al.*, 1994). However, the veterinary drugs meclofenamic acid and tolfenamic acid could not be detected at all. Therefore, it is likely that the detected antiphlogistics and lipid regulators arise predominately from human application underlined by the ubiquitous contamination of municipal STP discharges.

In a few STP effluents, acetylsalicylic acid, acetaminophen and dimethylaminophenazone were detectable (Table 4). Their maximum concentrations exceeded 1 $\mu g\,l^{-1}$, but the 90-percentile values were already not detectable or dramatically decreased. However, acetylsalicylic acid was detected in 22 of 49 STP effluents at concentrations up to 1.5 $\mu g\,l^{-1}$ and in rivers and streams up to 0.34 $\mu g\,l^{-1}$, although it is ultimately biodegradable in laboratory test systems as reported by Richardson and Bowron (1985). Acetaminophen was not present in surface waters above the detection limits, presumably due to high removal efficiencies of municipal STP. Above 98% have been eliminated in the investigated STP near Frankfurt/Main. Dimethylaminophenazone was detected in two samples of the river Main at concentrations up to 0.34 $\mu g\,l^{-1}$. Its approval as human drug in the European Union was withdrawn, because when it comes in contact with nitrite at an acidic pH, the carcinogenic dimethylnitrosamine is formed (Forth *et al.*, 1996). The presence of dimethylaminophenazone in municipal STP discharges may be caused by its low application level in veterinary medicine (Löscher *et al.*, 1994), but in the river Main the concentrations are more likely derived by industrial discharges.

Gentisic acid, a metabolite of acetylsalicylic acid as well as *o*-hydroxyhippuric acid and salicylic acid (Mutschler, 1996; Forth *et al.*, 1996) were not, or only sporadically found in municipal STP effluents. In the investigated STP near Frankfurt 98% elimination rate was observed. However, salicylic acid was only detected in 33 of 49 samples taken from river and stream waters, with a median concentrations of 0.2 $\mu g\,l^{-1}$. In addition to the (bio)degradation of acetylsalicylic acid other reasons for its observed concentrations may be a result of an application as an antioxidant agent, industrial STP discharges or natural occurrence may be possible to cause the observed concentrations. For example, salicylic acid was formed by sulfate-reducing bacteria obtained from a shallow anoxic aquifer by *o*-cresol degradation (Suflita *et al.*, 1989).

Due to the high application level of antiphlogistics indicated by high annual prescriptions (Table 1), and the opportunity to purchase most of them without prescription, their occurrence in the aquatic environment is plausible.

Betablockers and β_2-sympathomimetics. The betablockers metoprolol and propranolol, as well as betaxolol, bisoprolol and nadolol in smaller concentrations were detectable in STP discharges, and with the exception of nadolol additionally in rivers and streams (Table 5). However, only for metoprolol and propranolol median values in river and streams have been observed above the detection limits. The highest median values were found for metoprolol, with a concentration of 0.73 $\mu g\,l^{-1}$ in STP effluents and 0.45 $\mu g\,l^{-1}$ in the river and stream waters. The 90-percentile values of both matrices (above 1 $\mu g\,l^{-1}$) revealed that high concentrations of metoprolol were occasionally present in the aquatic environment, although it is mainly excreted as a metabolite. Obviously, the excretion rates of the unmetabolized drugs are sufficiently high to cause the observed environmental concentrations, because other application areas than that of medicine are not reported in literature. However, their principal excreted metabolites (e.g. metoprolol acid, 4-hydroxypropanolol, a-naphtoxylactic acid) are probably present in comparable concentrations (Balmér *et al.*, 1987; Walle *et al.*, 1988), but unfortunately they are not commercially available as reference compounds and must therefore be synthesized prior to analysis.

The β_2-sympathomimetics terbutalin and salbutamol were sometimes detectable in STP effluents, whereas clenbuterol and fenoterol were only detected in few cases. However, the concentrations of all β_2-sympathomimetics were extremely low and did not exceed 0.2 $\mu g\,l^{-1}$. In river and stream waters they were only sporadically present above the detection limit of 0.01 $\mu g\,l^{-1}$, with a maximum concentration of 0.061 $\mu g\,l^{-1}$.

Diazepam and two antineoplastics. Diazepam, a psychiatric drug, was present in 8 of 20 STP discharges at relative low concentrations amounting up to 0.04 $\mu g\,l^{-1}$. In river and stream waters diazepam was not detected above the determination limit of 0.030 $\mu g\,l^{-1}$ (Table 6).

The frequently in cancer chemotherapy applied antineoplastics ifosfamide and cyclophosphamide (Mutschler, 1996; Forth *et al.*, 1996) were detected in few municipal STP effluents, but not in the investigated rivers and streams (Table 6). All samples were analyzed by the method containing LC-electrospray/MS/MS. Detection limits were 0.010 $\mu g\,l^{-1}$ for both matrices. Cyclophosphamide was only present in STP discharges at concentrations up to 0.02 $\mu g\,l^{-1}$, whereas ifosfamide was observed in two samples above 0.08 $\mu g\,l^{-1}$. In the discharge of a STP, which is associated to a large university hospital, ifosfamide was detected with a concentration of 0.088 $\mu g\,l^{-1}$ and cyclophosphamide with 0.019 $\mu g\,l^{-1}$. Ifosfamide was present in the effluent of one additional rural municipal STP (connected to about 15,000 population equivalents), but surprisingly as high as 2.9 $\mu g\,l^{-1}$. Depending on the origin of the sewage exceptionally ifosfamide and cyclophosphamide can obviously be present in municipal STP discharges. However, a wide-spread presence was not observed and appears unlikely, because their application is mostly confined to chemotherapy in hospitals. Steger-Hartmann *et al.* (1996) found ifosfamide and cyclophosphamide in the sewage of a university hospital with concentrations of 0.024 $\mu g\,l^{-1}$ and 0.146 $\mu g\,l^{-1}$ respectively. They assumed that these anticancer agents are not degraded during passage through a STP, because a significant reduction did not occur in their laboratory-scale sewage treatment plant operated according to the modified OECD instruction 303A.

Carbamazepine. The antiepileptic drug carbamazepine was ubiquitously present in the aquatic environment. Carbamazepine showed a relatively high median value of 2.1 $\mu g\,l^{-1}$ in German STP effluents and 0.25 $\mu g\,l^{-1}$ in German river waters (Table 6). The highest maximum concentration detected for all drugs investigated in STP effluents was detected for carbamazepine at a concentration of 6.3 $\mu g\,l^{-1}$ and a 90-percentile value as high as 3.7 $\mu g\,l^{-1}$. Annual prescriptions of carbamazepine in Germany are as high as approximately 80 tons per year (Table 1). However, as revealed by pharmacokinetical data only 1–2% of carbamazepine is excreted unmetabolized. The major metabolite in humans is 10, 11 epoxy-carbamazepine, which is hydrolyzed further to diol-derivatives and are excreted principally as glucuronides (Frey and Janz, 1985; Hardman *et al.*, 1996). But additionally carbamazepine is inactivated by hydroxylation of the aromatic ring or *N*-glucuronidation at the carbamoyl moiety. These glucuronide-conjugates can presumably be cleaved in sewage and STP and thus increase the environmental concentrations. On the other hand the longer the medical treatment with carbamazepine the higher the efficiency of metabolization, because of auto-induction of the drug metabolizing enzymes (e.g. microsomale mono-oxygenase enzymes). If occasionally industrial discharges or even other application areas may increase the environmental concentrations, can yet not be concluded. However, the principal reason for the ubiquitously high carbamazepine concentrations appears to be the extremely low removal rate in municipal STP. Only 7% were removed in the selected STP near Frankfurt (Fig. 1). Although in the raw influent several drugs were present in comparable or even higher loads, in the discharge of the selected STP carbamazepine was found to be present with the highest average load (114 $g\,d^{-1}$).

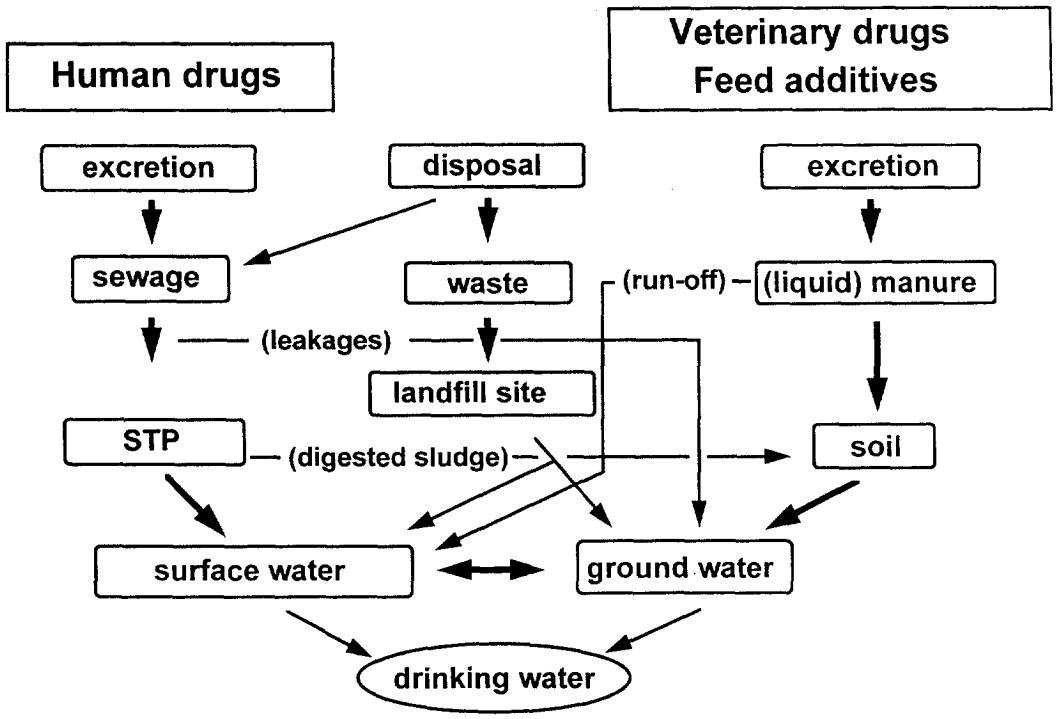

Fig. 3. Scheme for the main fates of drugs in the environment after application (STP: sewage treatment plant).

Fate of drugs in the environment

The detected drugs residues in German rivers and streams (Tables 3–6) presumably arise mainly from human applications, indicated by their widespread distribution in municipal STP. The fate of veterinary and human drugs after urinal or faecal

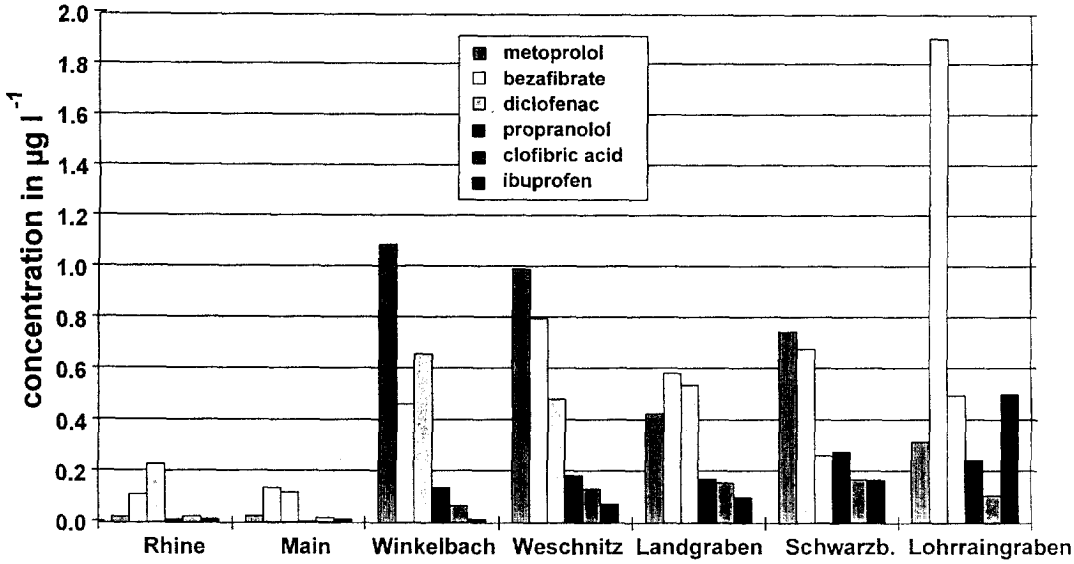

Fig. 4. Comparative contamination of small streams located in Hessisches Ried/Germany and the large rivers Rhine (Mainz) and Main (Bischofsheim) by selected acidic drugs and betablockers (Mean values of 14 d composite values of the Rhine (Mainz) from Jan. to Dec. 1996; mean values for random samples of the river Main (Bischofsheim) from Dec. 1996; mean values for random samples of streams at three sampling periods (April, September, October) in 1996.

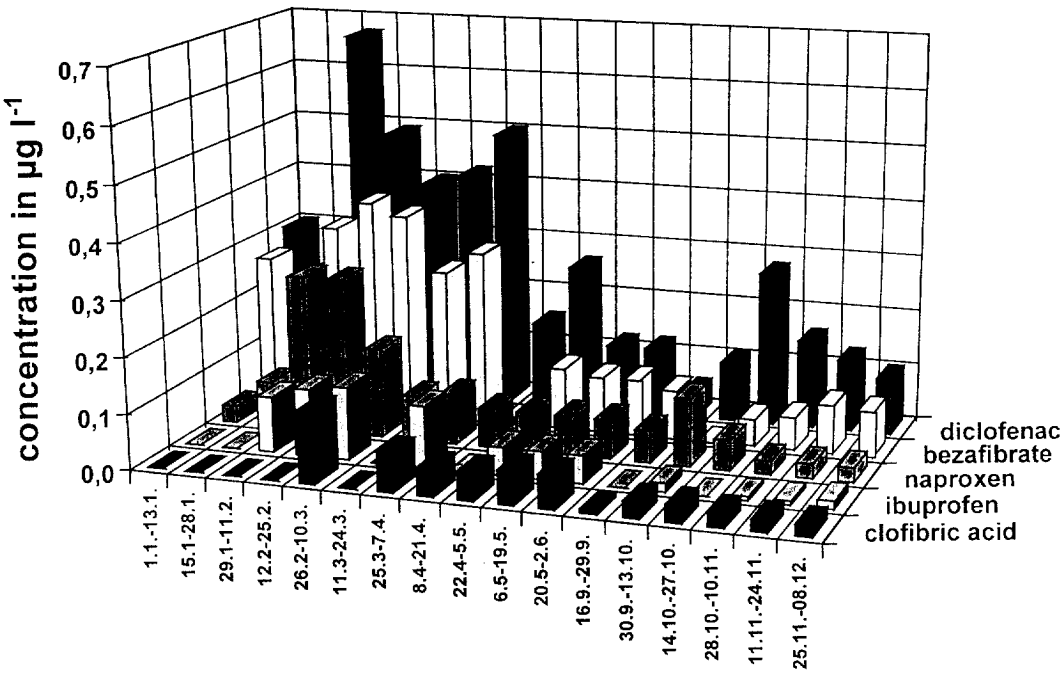

Fig. 5. Contamination of the river Rhine (Mainz) by acidic drugs in 1996 (14 daily composite samples taken at Mainz between January 1996 to June 1996 and September 1996 to December 1996).

excretion are quite different to each other. In general German municipal sewage and therefore excreted human pharmaceuticals have to pass through a STP prior to entering rivers or streams, whereas veterinary drugs are more likely to contaminate soil and ground water (without previous waste water treatment) when liquid manure is used for top soil dressing (Fig. 3). Additionally, after rainfall incidents surface waters can be polluted with human or veterinary drugs by run-off from fields treated with digested sludge or livestock slurries respectively. Industrial waste water may be another possible source for the contamination of surface waters (Richardson and Bowron, 1985), but are surely not responsible for their ubiquitous occurrence. Another possible contamination of soil and ground water may be caused by the application of digested sludge from municipal STP on agricultural areas. Additionally, transport of drugs via bank filtration from highly contaminated surface water into ground water is also a possibility, as the infiltration of waste waters directly from leakages in drains (Hall and Medmenham, 1992). Also drugs disposed together with domestic waste can reach landfill sites which could lead to ground water contamination by leaching (Holm *et al.*, 1995). A unique pathway for the contamination of soil and ground water by medicinal residues, derived from human application, may be the disposal of raw sewage or STP effluents by spray and broad irrigation in agricultural areas.

Table 7. Acidic drugs in the river Main (sampling date: Dec. 1996) at different distances between 77 and 4.5 km from its entry point into the river Rhine

(conc. in $\mu g\ l^{-1}$)	LOD*	77 km 12.12.96	56 km 12.12.96	46 km 13.12.96	34 km 13.12.96	26 km 14.12.96	16 km 14.12.96	4.5 km 15.12.96
Acetylsalicylic acid	0.020	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	0.020	n.d.	n.d.	n.d.	0.02	n.d.	0.02	0.03
Ibuprofen	0.020	n.d.	n.d.	n.d.	0.02	n.d.	n.d.	0.02
Gemfibrozil	0.020	n.d.	n.d.	0.02	0.03	n.d.	0.02	0.02
Fenoprofen	0.020	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ketoprofen	0.020	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	0.020	0.09	0.07	0.10	0.14	0.09	0.10	0.14
Fenofibric acid	0.020	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.03
Bezafibrate	0.10	0.10	n.d.	0.10	0.15	0.09	0.10	0.20
Indometacine	0.020	n.d.	0.02	0.03	0.03	n.d.	0.03	0.02

*Limit of detection, n.d.: not detectable.

Comparison of drug residues in large rivers and streams

Acidic drugs as well as the betablockers metoprolol and propranolol were found in small rivers and streams, as illustrated in Fig. 4, at higher concentrations as in the larger rivers, Rhine and Main. In general residues of acidic drugs in the river Rhine (Mainz) and Main (Bischofsheim) ranged from 0.05 $\mu g\,l^{-1}$ to 0.3 $\mu g\,l^{-1}$ (Fig. 5, Table 7). With the exception of phenazone and dimethylaminophenazone the maximum and 90-percentile concentrations of all drugs listed in Tables 3–6 were always observed in streams and not in rivers. Phenazone and dimethylaminophenazone were present in the river Main up to 0.95 $\mu g\,l^{-1}$, presumably mainly due to an industrial STP discharge. Additionally, a multitude of drugs (up to 20) were detectable in several investigated streams up to concentration greater than 6 $\mu g\,l^{-1}$. These streams, located in the Hessian Ried (center of Germany) contain a high percentage of STP discharges, as indicated by their relatively high boron concentrations, ranging from 0.25 to 1.0 $mg\,l^{-1}$ (Fooken *et al.*, 1997). Due to the fact that the STP discharges are highly contaminated by those drugs which are present in these streams, it can be assumed, that the enhanced percentage of municipal STP effluents are responsible for the elevated concentrations of the drugs (e.g. lipid regulating agents, betablockers). The run-off from agricultural areas, another potential source for the intake of drugs, was negligible in this region (Hessian Ried). Firstly, the amounts of digested municipal sludge applied to this area was very low and secondly run-off events are extremely seldom, due to the excellent permeability of the soils in large areas in this region (Berthold *et al.*, 1993).

ENVIRONMENTAL RISK ASSESSMENT

An environmental risk assessment for the drugs detected in river and stream waters was not undertaken, due to the lack of available ecotoxicological data (Römbke *et al.*, 1996). In the European Union physico-chemical data like Koc or Pow and in particular ecotoxicological data like LC_{50}, EC_{50} and NOEC are not mandatory for the governmental approval of human medicinal products. However, since January 1995 for the use of veterinary drugs in Germany an environmental risk assessment may be required before the approval is granted by the government, when significant exposure to drugs is expected and when the drug is potentially harmful to the environment. Additionally, pharmacokinetical studies have indicated that drugs are mainly excreted as metabolites. Due to their enhanced polarity, it can be assumed that the metabolites were often poorly eliminated during passage through a water treatment process of a STP. Hence, drug metabolites are expected to be present in the aquatic environment sometimes in comparable or even higher concentrations to the original (unchanged) drugs indicated by the environmental concentrations of clofibric acid and fenofibric acid. For the majority of the medicinal products including their metabolites an environmental risk assessment had never been carried out, although they are applied in the ton-range per year in medicine and are present in the environment presumably for many years.

The chemotherapeutic alkylating agents ifosfamide and cyclophosphamide may presumably be attributed to adverse environmental effects, due to their enormous side effects and their unspecific alkylating properties (Hardman *et al.*, 1996; Mutschler, 1996), but fortunately they were not detectable in rivers and streams above the detection limit of 10 $ng\,l^{-1}$. However, exceptions may occur as indicated by few contaminations of municipal STP discharges (Table 6).

Many drugs interact with human receptors (e.g. betablockers: antagonists of β-adrenergic receptors) when causing the required pharmacological effects. Aquatic vertebrates frequently have similar receptors which may be favorable for these drugs. However, the amounts of drugs in rivers and especially streams are several magnitudes lower compared to those applied in medicine; but it can not be ruled out that the multitude of drugs, which are present in rivers and streams, have adverse effects on aquatic organisms. Nevertheless, by these low environmental drug concentrations rather chronical effects may be caused than acute toxic effects.

CONCLUSIONS

The occurrence of a multitude of different drugs in German rivers and streams indicates the relatively high stability of these medicinal compounds under environmental conditions. Obviously, the common sewage treatment process is insufficient to completely eliminate these drug residues. Additionally, metabolites formed by conjugation (e.g. with glucuronic acid, sulfate) within phase II reactions are likely to be cleaved in the environment into the original (unchanged) pharmaceuticals (Richardson and Bowron, 1985), and hence may increase the relevant environmental concentrations. In Germany approximately 2900 drugs have approval for the use in human medicine (Rote Liste, 1994). The investigated 32 drugs and 5 metabolites represents only about 1% of the approved pharmaceutical compounds when considering human and veterinary drugs. However, the detected drugs were screened on the basis of their high prescriptions in human medicine, but it can be assumed that many other drugs and especially polar metabolites were present in the aquatic environment at concentrations up to the $\mu g\,l^{-1}$-range. Investigations about the contamination of different

ground water types by drug residues are currently under way.

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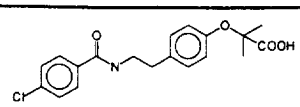
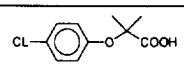
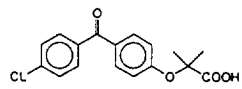
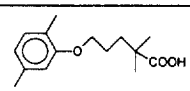
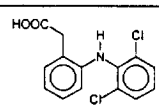
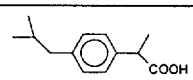
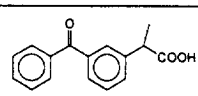
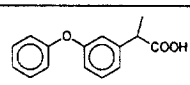
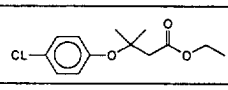
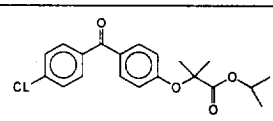
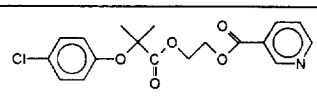
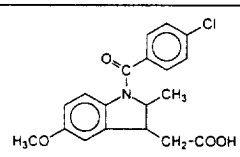
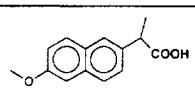
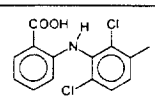
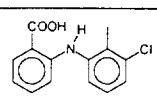
APPENDIX OVERLEAF

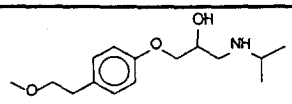
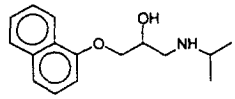
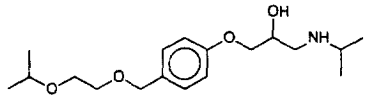
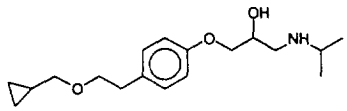
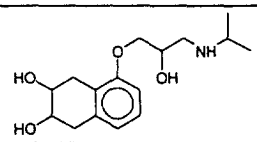
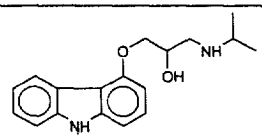
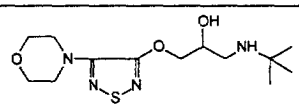
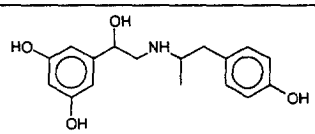
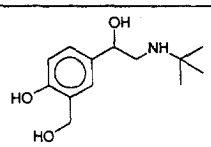
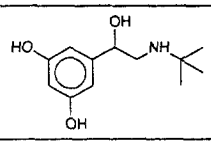
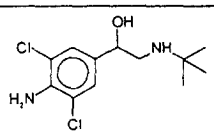
APPENDIX

Name, CAS-registration Number, Chemical Structures And Medicinal Classes Of The Analyzed Drugs

A1: Antiphlogistics, lipid regulating agents and corresponding metabolites

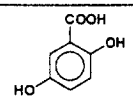
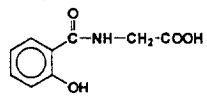
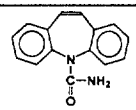
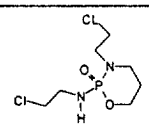
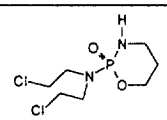
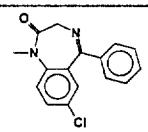
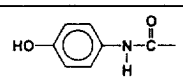
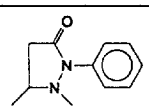
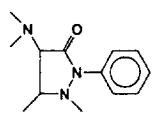
name	CAS-number	chemical structure	application
bezafibrate	41859-67-0		lipid regulating agent
clofibric acid	882-09-7		metabolite of lipid regulating agents
fenofibric acid	42017-89-0		metabolite of fenofibrate
gemfibrozil	25812-30-0		lipid regulating agent
diclofenac	15307-86-5		antiphlogistic
ibuprofen	15687-27-1		antiphlogistic
ketoprofen	22071-15-4		antiphlogistic
fenoprofen	53746-45-5		antiphlogistic
clofibrate	637-07-0		lipid regulating agent
fenofibrate	49562-28-9		lipid regulating agent
etofibrate	31637-97-5		lipid regulating agent
indometacine	53-86-1		antiphlogistic
naproxen	22204-53-1		antiphlogistic
meclofenamic acid	644-62-2		antiphlogistic
tolfenamic acid	13710-19-5		antiphlogistic

A2: Betablockers and β_2-sympathomimetics

name	CAS-number	chemical structure	application
metoprolol	37350-58-6		betablocker
propranolol	525-66-6		betablocker
bisoprolol	66722-44-9		betablocker
betaxolol	63659-18-7		betablocker
nadolol	42200-33-9		betablocker
carazolol	57775-29-8		betablocker
timolol	26839-75-8		betablocker
fenoterol	13392-18-2		β_2-symphatomimetic
salbutamol	18559-94-9		β_2-symphatomimetic
terbutalin	23031-32-5		β_2-symphatomimetic
clenbuterol	37148-27-9		β_2-symphatomimetic

—*continued overleaf*

A3: Metabolites of acetylsalicylic acid and neutral drugs of different medicinal classes

name	CAS-number	chemical structure	application
salicylic acid	69-72-7		metabolite of acetylsalicylic acid, keratolytic, dermatic, preservative of food
gentisic acid	490-79-9		metabolite of acetylsalicylic acid
o-hydroxy-hippuric acid	487-54-7		metabolite of acetylsalicylic acid
carbamazepine	298-46-4		antiepileptic drug
ifosfamide	3778-73-2		cytostatic agent
cyclophos-phamide	6055-19-2		cytostatic agent
diazepam	439-14-5		psychiatric drug
acetaminophen (paracetamol)	103-90-2		antiphlogistic
phenazone (antipyrine)	60-80-0		antiphlogistic
dimethylamino-phenazone (aminopyrine)	58-15-1		antiphlogistic