Determination of polar pharmaceuticals in sewage water of Greece by gas chromatography–mass spectrometry

ARTICLE *in* CHEMOSPHERE · MAY 2003

Impact Factor: 3.34 · DOI: 10.1016/S0045-6535(02)00819-6 · Source: PubMed

6 AUTHORS, INCLUDING:

Despina Tsipi
General Chemical State Laboratory of…
33 PUBLICATIONS **808** CITATIONS
SEE PROFILE

Anastasia Hiskia
National Center for Scientific Research…
80 PUBLICATIONS **2,359** CITATIONS
SEE PROFILE

PERGAMON

Chemosphere 51 (2003) 69–75

CHEMOSPHERE

www.elsevier.com/locate/chemosphere

Determination of polar pharmaceuticals in sewage water of Greece by gas chromatography–mass spectrometry ☆

V. Koutsouba [a], Th. Heberer [b], B. Fuhrmann [b], K. Schmidt-Baumler [b], D. Tsipi [a,*], A. Hiskia [c,*]

[a] General Chemical State Laboratory, Pesticide Residues Laboratory, An. Tsoha 16, 11521 Athens, Greece
[b] Institute of Food Chemistry, Technical University of Berlin, Gustav-Meyer-Allee 25, D-13355 Berlin, Germany
[c] Institute of Physical Chemistry, National Center for Scientific Research (NCSR) Demokritos, 15310 Athens, Greece

Received 26 June 2002; received in revised form 11 November 2002; accepted 25 November 2002

Abstract

Sewage influents and effluents of different urban areas of Greece, were analyzed for polar pharmaceutical residues, used in human medicine. Drugs investigated were the anti-inflammatory drugs diclofenac and ibuprofen, the metabolite of the drugs clofibrates used as blood lipid regulators, clofibric acid and the analgesics phenazone and propyphenazone. Analysis was carried out using capillary gas chromatography–mass spectrometry with selected ion monitoring. The method used was involved solid phase extraction (C_{18}) and derivatization with pentafluorobenzyl bromide. Diclofenac was detected in every sewage effluent sample.

Keywords: Drug residues; New environmental contaminants; Diclofenac

1. Introduction

Over the past decade, findings have been reported for drugs and drug metabolites of various therapeutical classes, used in human and veterinary medicine in effluents of wastewater treatments plants, surface, and groundwater in Europe and in the USA (Daughton and Ternes, 1999; Kolpin et al., 2002).

Pharmaceuticals are released in the environment mainly through human wastes by excretion of unmetabolized parent compounds and metabolites. Portions of the free excreted drugs and metabolites can escape elimination in the sewage treatment process (via wastewater treatment plants, or domestic septic systems) and enter the aquatic environment in sewage effluents (Daughton, 2001). Despite their continuous discharge in the environment, few data exists about the biodegradation, toxicity and environmental fate of pharmaceuticals (Halling-Sørensen et al., 1998).

Due to the polar structure of most pharmaceutical compounds they are not significantly adsorbed in the subsoil and may leach into the groundwater aquifers from the contaminated surface water (Heberer et al., 1997). Clofibric acid is the first prescription drug metabolite ever reported in sewage influent and effluent (Kansas City, USA in 1976) (Hignite and Azaznoff, 1977) and still the most frequently detected in sewage effluents, groundwater, surface and drinking water all over the world (Stan and Linkerhanger, 1992; Stan et al., 1994; Heberer and Stan, 1997; Buser et al., 1998a; Stumpf et al., 1999). Diclofenac and ibuprofen are used in human medical care belonging to the group of the nonsteroidal anti-inflammatory drugs. They are used

☆ Part of this work was presented in the 219th American Chemical Society National Meeting, San Francisco (CA) 26-31/3/2000.

* Corresponding authors. Tel.: +30-10-6503643; fax: +30-10-6511766.

E-mail address: hiskia@chem.demokritos.gr (A. Hiskia).

0045-6535/03/$ - see front matter
doi:10.1016/S0045-6535(02)00819-6

worldwide with a production volume estimated to be in the hundreds of tons annually. These drugs have been detected in sewage effluents, surface and groundwater in Germany (Heberer et al., 1998; Ternes, 1998), in Swiss (Buser et al., 1998b, 1999) and effluent sewage waters in Brazil (Stumpf et al., 1999). The analgesics phenazone and propyphenazone have been detected in Berlin sewage treatment works (Heberer et al., 1997; Ternes, 1998). Analgesics of the phenazone type, including propyphenazone, were also determined in soil and groundwater below the main municipal solid wast landfill of the city of Zagreb, Croatia (Ahel and Jelicic, 2001).

Various multi-residue analytical methods for the determination of polar drug residues in aqueous solutions have been described in literature using gas chromatography–mass spectrometry (GC–MS) detection after derivatization by diazomethane (Ternes et al., 1998; Ollers et al., 2001). However, preparation and use of diazomethane carries some risk and reasonably skilled technicians can carry out these procedures safety. Recently, alternative methods involving liquid chromatography–mass spectrometry (LC–MS) have been developed for the analysis of polar drugs in aqueous environmental samples (Farre et al., 2001; Ternes, 2001; Miao et al., 2002). However, LC–MS are costly instruments therefore their use is not always available for routine analysis.

In this study the occurrence of five polar pharmaceuticals, namely clofibric acid, diclofenac, ibuprofen, phenazone and propyphenazone was investigated in treated and untreated sewage, in Greece within a Hellenic-German joint project (Hellenic-German Scientific Cooperation, 1997–1999).

Although prescription numbers of the investigated drugs were unavailable, as they can be purchased in a pharmacy without prescription, it can be estimated that the annual consumption is high, due to their intensive use and the relatively high therapeutical dosages (Buser et al., 1998a,b, 1999).

The analytical method performed, involves solid phase extraction (SPE) of the target analytes and determination by capillary GC–MS with selected ion monitoring (SIM), after derivatization with pentafluorobenzyl bromide (PFBBr). The method initially developed for the determination of acidic herbicides and related polar contaminants (Butz et al., 1994; Heberer et al., 1994) has been extended to pharmaceuticals and its potential is demonstrated in heavily polluted sewage samples.

The aim of this work was to obtain a first overview of possible contamination of sewage water of Greece from pharmaceuticals.

2. Experimental

2.1. Materials

All drugs (clofibric acid, diclofenac, ibuprofen, phenazone, propyphenazone) and 2,4-dichlorobenzoic acid (Fig. 1) were with purity 99%, purchased from Sigma (St. Louis, MO, USA), Ferak (Berlin, Germany) and Promochem (Wesel, Germany). 3,4-Dichlorophenoxyacetic acid (3,4-D) was donated by the Technical University of Berlin, Institute of Food Chemistry, Germany. Pesticide grade (pestiscan) acetone, methanol and toluene were provided by Lab-scan (Dublin, Ireland). PFBBr and triethylamine were obtained from Sigma (St. Louis, MO, USA). Bakerbond SPE Polar Plus C_{18} were products of Baker (Phillipsburg, NG, USA). High purity water provided by ultrapure water system (nanopure UV).

2.2. Sampling

Samples were collected from different areas of Greece with high municipal sewage outputs. The sewage treatment plants were situated in Athens (Metamorphossi and Psitalia), Thessaloniki, Ioannina and Heraklion in

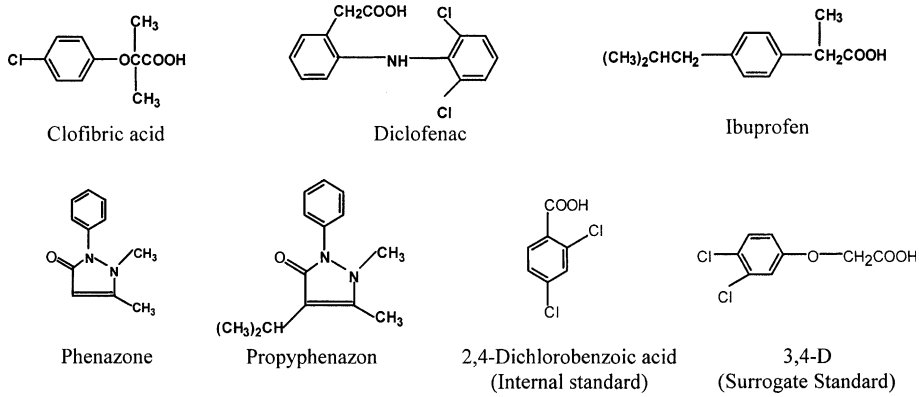

Fig. 1. Structures of the drugs investigated, surrogate and internal standard.

Table 1
RT windows for SIM ions

RT window	Time (min)	Compounds	SIM ions	Mass window
1	16.00–18.00	Phenazon	77, 96, 188	1.0
2	18.00–20.00	Clofibric acid	128, 130, 394	1.0
		Propyphenazone	96, 215, 230	
		2,4-Dichlorobenzoic acid (ISTD)	173, 370, 372	
3	20.00–24.30	Ibuprofen	161, 343, 386	1.0
4	24.30–34.90	3,4-D (surrogate standard)	175, 400, 402	1.0
5	34.90–50.50	Diclofenac	214, 216, 475	1.0

Crete island. The samples were sewage influents and effluents collected at least every two days. They were collected in 2 l glass bottles and kept refrigerated (0–4 °C) during transportation to the laboratory, where they remained refrigerated (4 °C) until analysis. The time between sampling and analysis was not more than three days. Preservation agents were not used during storage.

2.3. Sample preparation

All sewage samples, influents and effluents, were filtered through a 0.45 μm glass fiber filter (millipore) to remove particulate material. A sample of 1 l was mixed with a solution of 3,4-D in methanol (1 mg l^{-1}) as surrogate standard to give a concentration of 100 ng l^{-1} and then acidified to pH < 2 with HCl. The water sample was applied to a C_{18} cartridge, previously conditioned with 10 ml acetone, 10 ml methanol and finally 10 ml of distilled, deionized water (pH < 2). Then, it was percolated through the cartridge at a maximum flow-rate of approximately 8 ml min^{-1} by applying a low vacuum. After drying the cartridge for 2–3 h under a gentle stream of nitrogen, the analytes were eluted with 2.5 ml of methanol. The eluate from the SPE cartridge containing the target compounds was mixed with 100 μl of a solution of 2,4-dichlorobenzoic acid in methanol (2 mg l^{-1}), as internal standard and dried under a gentle stream of nitrogen. The sample eluate was derivatized by adding 200 μl of PFBBr (2%, in toluene) and 5 μl triethylamine, as catalyst, in a sample vial that was sealed with caps containing Teflon lined septa and was put at 110 °C in a drying cabinet for 1 h. The derivatized sample was dried under nitrogen and finally dissolved in 100 μl of toluene.

2.4. Chromatographic analysis

Analyses for this study were performed on a Finnigan Mat GCQ GC/ITD-MS fitted with a 30 m × 0.25 mm i.d. × 0.25 μm Hewlett Packard HP-5 MS capillary column. Carrier gas was helium (purity: 99.999%) and the flow rate was held at constant velocity of 40 cm s^{-1}. The oven temperature was held at 100 °C for 1 min following injection, then programmed at 30 °C min^{-1} to 150 °C, which was held for 1 min, then at 3 °C min^{-1} to 205 °C followed by 10 °C min^{-1} to 260 °C and finally held for 23 min (total run time of 50.50 min). The transfer line was set at 275 °C and the ion source at 200 °C. Electron energy for the filament was set at 70 V. The ITD settings were as follows: mass range 50–500 (for full scan only), microscans 3, max ion time 25 ms. 2 μl of sample were injected splitless at an injector temperature of 250 °C with a splitless time of 0.8 min on. The MS system was tuned before each sequence run.

For SIM operation, five retention time (RT) windows were used, each recording the ions selected for the eluting derivatized drugs, as presented in Table 1.

3. Results

3.1. Determination

The pentafluorobenzyl (PFB) derivatives of target compounds, i.e. phenazone, clofibric acid, propyphenazone, 2,4-dichlorobenzoic acid (internal standard, ISTD), ibuprofen, 3,4-D (surrogate standard) and diclofenac were determined by capillary GC ion trap-mass spectrometry in EI mode of operation.

Typical chromatograms are shown in Fig. 2 for a sewage sample, spiked from 500 to 1000 ng l^{-1} per analyte, using full-scan conditions (B) and time-scheduled SIM (C) under EI mode. As compiled in Table 1, for chromatograms recorded under time-scheduled SIM three characteristic ions were selected for each compound and scanned using corresponding time windows. The time-scheduled SIM chromatogram shows better baseline stability and fewer peaks than the corresponding one with full-scan acquisition.

The matrix interference during analysis of target compounds in pure water and sewage samples in the GC–MS system was under consideration. In real samples the matrix ions in full-scan mode overload the spectrum of the target analytes resulting difficulties to the detection. As it is shown in Fig. 2(B), phenazone in sewage can hardly be traced due to the high background

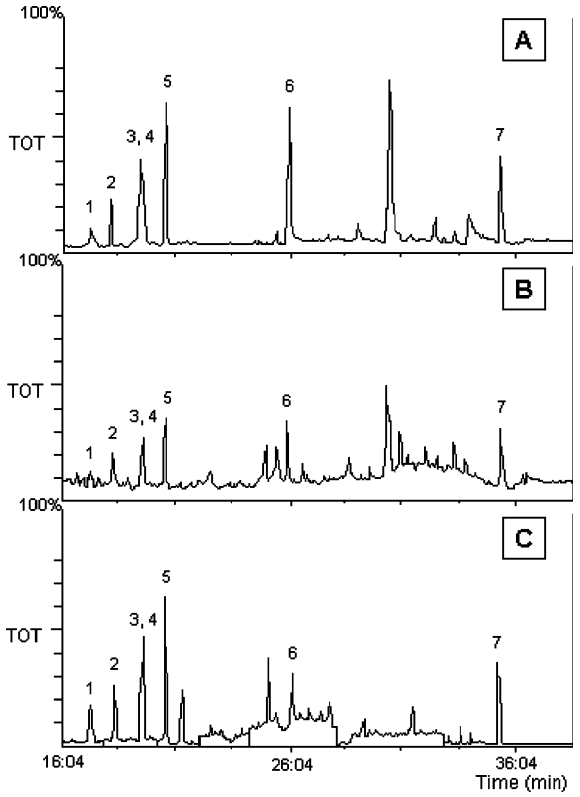

Fig. 2. (A) Full-scan chromatogram of a spiked sample obtained in pure water, from 500 to 1000 ng l^{-1}. (B) Full-scan chromatogram of a spiked sewage sample from 500 to 1000 ng l^{-1}. (C) SIM chromatogram of a spiked sewage sample from 500 to 1000 ng l^{-1}. (1) Phenazone, 500 ng l^{-1}; (2) Clofibric acid, 500 ng l^{-1}; (3) Propyphenazone, 500 ng l^{-1}; (4) 2,4-Dichlorobenzoic acid (ISTD), 200 ng l^{-1}; (5) Ibuprofen, 1000 ng l^{-1}; (6) 3,4-D (surrogate standard), 100 ng l^{-1} and (7) Diclofenac, 1000 ng l^{-1}.

with a signal to noise ratio of 3, while in the chromatogram from pure water sample, at the same fortification level, it could be detected with a signal to noise ratio of 35 respectively (Fig. 2(A)). The noise levels were always lower under SIM conditions with better signal to noise ratio for all target analytes in fortified sewage samples, indicating that sensitivity is better comparing to full-scan conditions. In the case of phenazone, the signal to noise ratio was 47 and no other peak was observed in the time window selected for its confirmation (Fig. 2(C)), thus making the difference between the acquisition modes.

Quantitation was performed under time scheduled SIM conditions using the ratio of the total abundance of the characteristic ions of each analyte, referred in Table 1, to the total abundance of the characteristic ions of the internal standard 2,4-dichlorobenzoic acid. The calculation of the results was performed using internal standard (2,4-dichlorobenzoic acid) calibration. The detector response for all target compounds was linear in the concentration range studied from 10 to 2000 ng l^{-1} under SIM conditions and the correlation coefficients were better than 0.998.

The poor resolution of propyphenazone and the 2,4-dichlorobenzoic acid PFB derivatives (Fig. 2(C) peaks 3 and 4) does not cause any problem in the selectivity of the detection method. These two analytes were unequivocally identified by their characteristic ion traces, considering also their abundance ratios.

An application of the above procedure in a contaminated sewage sample is shown in Fig. 3. Fig. 3(A) shows the SIM chromatogram of a pentafluorobenzylated extract of an effluent sample from the Heraklion sewage plant taken on 8/6/1999. The positive confirmation of the identity and the quantitation (299 ng l^{-1}) of the analyte diclofenac was performed by means of the three indicative ion traces that are the source of the peak seen in the SIM chromatogram (Fig. 3(B)).

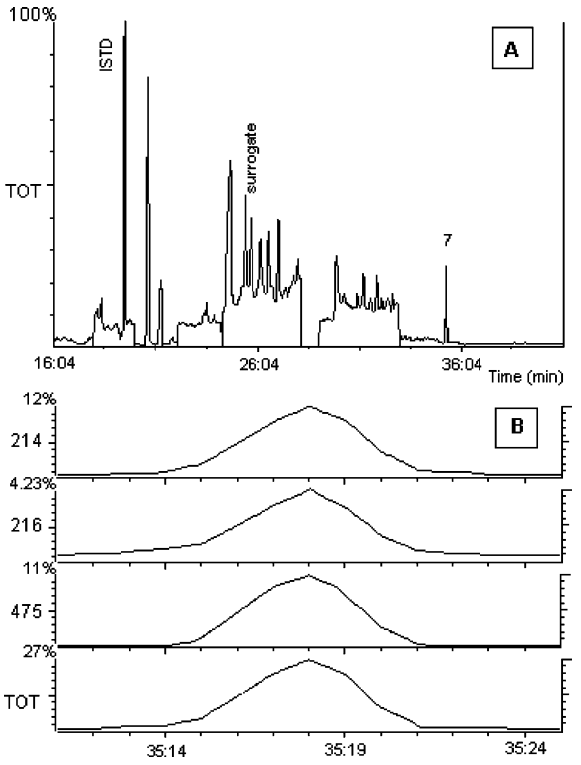

Fig. 3. (A) Chromatogram recorded with GC–MS applying SIM of a sewage effluent sample collected from the sewage plant Heraklion (8/6/99). 2,4-Dichlorobenzoic acid (ISTD), 3,4-D (surrogate standard) and diclofenac (7). (B) Indicative ion traces for the PFB-ester of diclofenac extracted from the SIM chromatogram shown in Fig. 3(A).

3.2. Method validation

The proposed method was validated by carrying out recovery experiments establishing the method accuracy and precision. For the recovery experiments, sewage water samples (1 l), were fortified with a mixture of the five drugs, at a concentration level of 1000 ng l^{-1}. Surrogate standard 3,4-D was added at a concentration of 100 ng l^{-1}. The surrogate standard was used to check the recovery process of target analytes in the analysis of real samples. In the case that surrogate recovery value was not acceptable the whole procedure was repeated.

The results of the recovery experiments (in triplicate) obtained after extraction of the target compounds from sewage samples, are presented in Table 2. The mean recoveries were between 67% and 90% approaching successful recovery in most cases. The precision of the method expressed by the relative standard deviation (RSD) of the mean recovery values, when triplicate spiked sewage samples were analyzed, was better than 18%.

The limits of detection (LOD) of the studied compounds were calculated by selecting the lowest concentration of the spiked sample that produces a chromatographic peak having a height equal to three times the standard deviation of the baseline noise of the blank sample. For the calculation of each LOD the Knoll equation was used (Knoll, 1985): $C_{LOD} = K_{LOD} h_n C_s / h_s$, where C_{LOD} is the LOD quantity, h_s/C_s is the analyte peak height/unit amount of analyte, h_n is the largest noise fluctuation (either positive or negative) observed in the noise measurement interval and K_{LOD} is a constant, determined for the measurement interval employed. The limits of quantitation (LOQ) for each analyte were determined from the equation $C_{LOQ} = K_{LOQ} h_n C_s / h_s$ (Knoll, 1985), where C_{LOQ} is the LOQ quantity, h_s/C_s and h_n are the same as above and K_{LOQ} is a constant, determined for the measurement interval employed. Their values in full-scan and SIM conditions are shown in Table 3.

In the full-scan acquisition mode, the LODs were in the range of 36–340 ng l^{-1}, whereas in the SIM acquisition mode they were in the range of 0.6–20 ng l^{-1} respectively. From the comparison between the two modes of acquisition, it can be seen that there is always a great difference between the LODs obtained in SIM conditions and those obtained in full-scan conditions. The lower SIM LODs makes SIM conditions to be preferable in terms of detectability, in the analysis of heavily polluted water samples.

Table 2
Mean % recovery ± RSD of five drugs at fortification level of 1000 ng l^{-1} ($n = 3$)

Compounds	Mean % recovery ± RSD
Phenazon	82 ± 11
Clofibric acid	90 ± 15
Propyphenazone	69 ± 7
Ibuprofen	67 ± 18
3,4-D (surrogate standard)	113 ± 16
Diclofenac	76 ± 9

3.3. Monitoring data

The study of a possible contamination of sewage effluents with the five target drugs was carried out in 1998 and 1999. 22 samples of sewage effluents were collected from five sewage treatment plants of Greece, namely Psittalia (Athens), Metamorfossi (Athens), Thessaloniki, Ioannina, Heraklion (Crete). These sewage treatment plants collect more than 50% of the total municipal sewages. The extent to which a particular plant uses primary and secondary technology greatly influences removal efficiencies. The technologies employed vary among cities. Sewage effluents are discharged directly or through rivers into the Mediterranean Sea.

The findings of the study are presented in Table 4.

Diclofenac was identified as pharmaceutical residue in the influents and effluents of all sewage plants at concentration up to 560 and 365 ng l^{-1}, respectively. These concentrations are in the range of those reported from wastewater treatment plant installations in Switzerland (Buser et al., 1998a,b) and Germany (Ternes

Table 3
LOD and LOQ in full-scan and SIM mode of operation

Compounds	Mode of operation			
	Full-scan		SIM	
	LOD (ng l^{-1})	LOQ (ng l^{-1})	LOD (ng l^{-1})	LOQ (ng l^{-1})
Phenazone	340	990	20	60
Clofibric acid	244	714	1.8	5
Propyphenazon	256	748	3.8	10
Ibuprofen	36	104	0.6	1.6
Diclofenac	38	108	1	2

Table 4
Results of the Greek sewage water monitoring for pharmaceutical residues

Compounds	Influent/effluent	Number > LOQ	Concentration range in #positive samples ($ng\,l^{-1}$)
Phenazon	Influents	0 of 11	
	Effluents	0 of 11	
Clofibric acid	Influents	0 of 11	
	Effluents	1 of 11	5
Propyphenazone	Influents	3 of 11	10–200
	Effluents	0 of 11	
Ibuprofen	Influents	0 of 11	
	Effluents	0 of 11	
Diclofenac	Influents	11 of 11	12–560
	Effluents	11 of 11	10–365

et al., 1998). The propyphenazone identified in three influent samples, was not found in any of the effluents. Chlofibric acid, which has been found in sewage, surface and drinking water in Berlin was with one exception (5 $ng\,l^{-1}$ in Metamorfossi effluent on 17/11/98) not detected in Greece. The drugs ibuprofen and phenazone were not identified in none of the samples.

4. Conclusion

The results of our monitoring indicated that all sewage influent and effluent water samples were found contaminated with diclofenac, at concentration in the range of those reported in other European countries. The occurrence of diclofenac in all municipal sewage treatment plant influents, points to human usage and has no correlation to industrial discharges. As we found diclofenac in every effluent sample, we assume that it is not completely eliminated during passage through the sewage treatment plant and enters the receiving waters.

The described method enabled the determination of the target pharmaceuticals in highly contaminated water samples, such as sewage water, even at concentrations down to the low nanogram per litre level.

The detection of target analytes in Greek sewage effluents documented that the occurrence of drugs in the environment is a global environmental issue. It can be speculated that other high-volume pharmaceutical compounds with appropriate physicochemical properties may also lead to detectable concentration in surface waters and possible environmental contamination via sewage. Although the concentrations found were very low ($ng\,l^{-1}$), orders of magnitude below therapeutic threshold levels, much is yet to be learned relating to the effects (particularly those chronic in the environment) on humans, plants and animals exposed to low level concentrations of pharmaceuticals.

Acknowledgements

This study was conducted within the activities related to the Joint Project GRI-161-97. The authors wish to thank the Hellenic-German Scientific Cooperation for supporting this field.

References

Ahel, M., Jelicic, I., 2001. Phenazone analgesics in soil and groundwater below a municipal solid waste landfill. In: Daughton, C.G., Jones-Lepp, T. (Eds.), Pharmaceuticals and Personal Care Products in the Environment. In: Scientific and Regulatory Issues, ACS Symposium Series 791. American Chemical Society, Washington DC, pp. 100–115.

Buser, H.-R., Muller, M., Theobald, N., 1998a. 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., Muller, M., 1998b. 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., Muller, M., 1999. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environ. Sci. Technol. 33, 2529–2535.

Butz, S., Heberer, Th., Stan, H.-J., 1994. Determination of phenoxyalkanoic acids and other acidic herbicides at the low ppt level applying solid-phase extraction with RP-C 18 material. J. Chromatogr. A 677, 63–74.

Daughton, C., 2001. Pharmaceuticals and personal care products in the environment: overarching issues and overview. In: Daughton, C.G., Jones-Lepp, T. (Eds.), Pharmaceuticals and Personal Care Products in the Environment. In: Scientific and Regulatory Issues, ACS Symposium Series 791. American Chemical Society, Washington DC, pp. 2–38.

Daughton, C., Ternes, T., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ. Health Perspect. 107, 907.

Farre, M., Ferrer, I., Ginebreda, A., Figueras, M., Ollivella, L., Tirapu, L., Vilanova, M., Barcelo, D., 2001. Determination of drugs in surface water and wastewater samples by liquid chromatography–mass spectrometry: methods and preliminary results including toxicity studies with *Vibrio fischeri*. J. Chromatogr. A 938, 187–197.

Halling-Sørensen, B., Nielsen, S.N., Lanzky, P.F., Ingerslev, F., Holten Lutzheft, H.C., Jørgensen, S.E., 1998. Occurrence, fate and effects of pharmaceutical substances in the environment: a review. Chemosphere 36, 357–394.

Heberer, Th., Stan, H.-J., 1997. Determination of clofibric acid and *N*-(phenylsulfonyl)-sarcosine in sewage, river and drinking water. Int. J. Environ. Anal. Chem. 67, 113–124.

Heberer, Th., Butz, S., Stan, H.-J., 1994. Detection of 30 acidic herbicides and related compounds as their pentafluorobenzylic derivatives using gas chromatography/mass spectrometry. J. AOAC Int. 77, 1587–1604.

Heberer, Th., Dunnbier, U., Reilich, Ch., Stan, H.-J., 1997. Detection of drugs and drug metabolites in ground water samples of a drinking water treatment plant. Fresenius Environ. Bull. 6, 438–443.

Heberer, T., Schmidt-Baumler, K., Stan, H.-J., 1998. Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part I: Drug residues and other polar contaminants in Berlin surface and ground water. Acta Hydrochim. Hydrobiol. 26, 272–278.

Hellenic-German Scientific Cooperation, 1997–1999. Investigation and determination of new environmental contaminants in Greek surface water. European Union Project GRI-161-97.

Hignite, C., Azaznoff, D.L., 1977. Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Sci. 20, 337–342.

Knoll, J.E., 1985. Estimation of the limit of detection in chromatography. J. Chromatogr. Sci. 23, 422.

Kolpin, D., Furlong, E., Meyer, M., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999–2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1271.

Miao, X.S., Koenig, B.G., Metcalfe, C.D., 2002. Analysis of acidic drugs in the effluents of sewage treatment plants using liquid chromatography–electrospray ionization tandem mass spectrometry. J. Chromatogr. A 952, 139–147.

Ollers, S., Singer, H.P., Fasser, P., Muller, R., 2001. Simultaneous quantification of neutral and acidic pharmaceuticals and pesticides at the low-ng/l level in surface and waste water. J. Chromatogr. A 911, 225–234.

Stan, H.-J., Linkerhanger, M., 1992. Identifizierung von 2-(4-chlorphenoxy)-2-methyl-propionsäure im Grundwasser mittels Kapillar-Gaschromatographie mit Atomemissionsdetektion und Massenspektrometrie. Vom Wasser 79, 75–88.

Stan, H.-J., Heberer, Th., Linkerhgner, 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.

Stumpf, M., Ternes, T.A., Wilken, R.-D., Rodriguesb, S.V., Baumann, W., 1999. Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. Sci. Total Environ. 225, 135–141.

Ternes, T.A., 1998. Occurrence of drugs in german sweage treatment plants and rivers. Water Res. 32, 3245–3260.

Ternes, T.A., 2001. Analytical methods for the determination of pharmaceuticals in aqueous environmental samples. Trends Anal. Chem. 20, 419–433.

Ternes, T.A., Stumpf, M., Schuppert, B., Haberer, K., 1998. Simultaneous determination of antiseptics and acidic drugs in sewage and river water. Vom Wasser 90, 295–309.