ELSEVIER

Journal of Hazardous Materials 122 (2005) 195–204

Journal of Hazardous Materials

www.elsevier.com/locate/jhazmat

Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden

David Bendz [a,*], Nicklas A. Paxéus [b], Timothy R. Ginn [c], Frank J. Loge [c]

[a] *Swedish Geotechnical Institute, Department of Environmental Technology, Hospitalsgatan 16A, S-211 33 Malmö, Sweden*
[b] *Gryaab, Karl IX:s väg, S-418 34 Gothenburg, Sweden*
[c] *University of California, Department of Civil and Environmental Engineering, 1 Shields Avenue, 2001 Engineering III, Davis, CA 95616, USA*

Available online 21 April 2005

Abstract

Pharmaceutically active compounds (PhACs) in the environment lately have been acknowledged to constitute a health risk for humans and terrestrial and aquatic ecosystems. Human and veterinary applications are the main sources of PhACs in the environment and the major pathways are excretion and discharge to the environment through sewage treatment plants (STPs). In this study, the occurrence and fate of selected human PhACs belonging to different therapeutic classes (non-steroidal anti-inflammatory drugs, lipid regulators, anti-epileptics, antibiotics and β-blockers) were investigated in a small river in the very south of Sweden. The objectives of the study were to evaluate the impact of a high and rather constant load in sewage influent on downstream concentrations and whether substances that are metabolized to a high degree in humans also show a low persistency in a natural aquatic environment. Water samples were collected from the influent and effluent of the STP, in a series of dammed reservoirs leading to discharge into the Höje River in Sweden, and at several locations in the river downstream of the outfall. After enrichment by solid-phase extraction, the compounds were analyzed using GC–MS (methylated derivatives) or LC–MS/MS. In addition to the targeted pharmaceuticals, GC–MS analysis of the samples revealed the presence of other sewage-related pollutants (triclosan, caffeine, flame-retardants, antioxidants) and these results where included for comparison. Removal efficiencies were calculated in the STP and found to display a wide range with numerous species surviving treatment at greater than half their influent concentrations, including diclofenac, the anti-epileptic carbamazepine, a β-blocker (propanolol), and antibiotics trimetoprim and sulfamethoxazole. Low removals were also observed for Tris(2-chloroisopropyl)phosphate (flame retardant), BHT-aldehyde (oxidation product of BHT) and synthetic musk (HHCB). The concentrations of chloride (Cl^-) and boron (B) were used as natural inert tracers to estimate the relative extent of dilution of PhACs measured in the effluent of the STP on concentrations measured further downstream. Based on spatial trends of concentrations (recalculated to reflect a hypothetical scenario with no dilution), ibuprofen, ketoprofen, naproxen and dicofenac were shown to be subject to significant abiotic or biotic transformations or physical sequestration in the river. The β-blockers atenolol, metoprolol and propanolol, the antibiotics trimetoprim and sulfametoxazole, and carbamazepine demonstrated a high degree of persistence. Fluctuations in the concentration of carbamazepine and gemfibrozil were observed along the series of reservoirs and within the river and are hypothesized to be due to release of parent compound from glucuronides. Several of the investigated substances (metaprolol, propanolol and carbamazepin) that exhibit low excretion rates as parent compounds demonstrate a surprising persistence in the aquatic environment. It is concluded that pharmaceutical substances with a high metabolic rate in humans (low excretion rate) do not necessarily induce a short lifetime in aquatic environments. Results from this study emphasize the need for a broader view on the concept of persistence that accounts for loading rates, in addition to removal mechanisms (e.g., transformation, volatility and physical sequestration by solids), under a variety of spatial and temporal scales.

Keywords: Pharmaceutical; Transport; Persistence; Sewage; Recipient

1. Introduction

Pharmaceutically-active compounds (PhACs) in the environment lately have been acknowledged to constitute a major health risk for humans and members of terrestrial and aquatic

* Corresponding author. Tel.: +46 40 35 67 76; fax: +46 40 93 86 85.
E-mail address: David.Bendz@swedgeo.se (D. Bendz).

0304-3894/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jhazmat.2005.03.012

ecosystems. Human and veterinary applications are the main sources of PhACs in the environment that are introduced primarily through excretion and the subsequent transport in sewage, whereas direct disposal of unwanted or expired drugs in the sewage is believed to be of minor importance [1]. In the comprehensive reviews [1–5], the available data on the occurrence of PhACs in sewage, sludge, sediments, oceans, rivers, and landfill leachate [6–8] are compiled. In comparison with conventional priority pollutants, these substances are designed to have specific pharmacological and physiological functions and thus are inherently potent, often with unintended health outcomes in wildlife. Many PhACs do not exhibit an acute aquatic toxicity but have a significant cumulative effect on the metabolism of nontarget organisms [3] and the ecosystem as a whole [2]. Paramount among these are compounds that interfere with natural hormones, i.e. endocrine disruptors, in nontarget species that act either by design or unintended effect. As an instance of the latter, the feminization of gull embryos associated with exposure to the pesticide DDT [9], is one of the earliest reports of unintended endocrine disruption resulting from environmental contaminants. This and numerous other instances are reviewed in [10]. Many endocrine disruptors induce serious effects in low concentrations [1,3,11] but also individual PhACs occurring in low concentrations may exhibit synergistic and cumulative effects. In addition, the development of antibiotic resistance may be stimulated in bacteria from exposure to low concentrations [11].

Sewage treatment plants (STPs) play a crucial role in the separation of PhACs into two exposure pathways associated with the aquatic and the solid phase and the subsequent introduction into the environment. Partitioning between phases depends in part on the degree of polarity of the particular compound. Sludge material and consequently terrestrial environments are likely to be the destination for less polar or nonpolar substances, whereas the polar substances are expected to remain primarily in the aqueous phase. A large number of PhACs are polar and neither volatile nor biodegradable, thus escaping sedimentation and biological treatment in STPs [12]; these compounds represent the bulk of the load into aquatic environments. In addition, substances with low solubility can bypass STPs due to colloid-facilitated transport [2] during periods of high effluent turbidity. Overflow due to technical problems, floods, or high influent loads may also cause substances with low solubility to shortcut the STPs [12]. Specific removal processes and efficiencies of STPs are largely unknown because it is not possible to distinguish between [2]:

- degradation to lower molecular weight compounds;
- physical sequestration by solids (and subsequent removal with sludge);
- transformation into conjugates that can later be hydrolyzed to yield the parent compound. Conjugates can act as reservoirs from which the free drugs can later be released into the environment.

Because PhACs generally pass through STPs [3], cumulative effects may be unintentionally incurred and magnified by "reuse" of such waters through pond infiltration into groundwater aquifers or where STP effluent contributes significantly to flow in natural rivers. Whether or not the bioavailable concentrations of PhACs in such systems are cause for concern depend on both the loading and the field-scale fate and transport mechanisms involved.

The fate and transport of PhACs in natural aquatic environments is poorly understood [3,4,10] and no comprehensive study has been conducted to date [5]. With the exception of a limited number of studies of antibiotics [13–16], very few data (e.g., [17]) exist on the fate (degradation and sorption) of pharmaceuticals in natural porous media. Contrary to the temporal emission pattern of conventional priority pollutants, the environmental load of PhACs is generally constant and widely distributed. Although some PhACs may have a low persistence, the constant load may dominate over the transformation rate. Furthermore, the interaction of solute PhACs with natural sediments may provide for a sink of these compounds and for distribution of residence times of unknown consequences for exposure. Daughton and Ternes [2] argue that the concept of persistency has to be redefined to reflect the ratio of "transformation rate" to "supply rate" instead of looking solely at the transformation rate as is done for conventional priority pollutants.

Building upon this statement [2], the objectives of this study were to: (1) assess the impact of a high and rather constant load of PhACs in sewage influent on downstream concentrations, and (2) evaluate whether substances that are metabolized to a high degree in humans also are degraded comparably fast in the natural aquatic environment [18]. Specific PhACs were selected for this study based on their exclusive use in Sweden for human consumption, environmental concern (toxicity), and therapeutic category; in addition, the compounds were selected to represent varying polarity and bioavailability to encompass the range of characteristics influencing fate in a natural aquatic environment. Two substances that were not expected in Sweden sewage were also selected for analyses in this study, clofibric acid (no parent drugs producing this metabolite are sold in Sweden) and flurbiprofen, based on use throughout the European continent. In addition to pharmaceuticals, GC–MS analysis targeted triclosan, caffeine, flame-retardants, and antioxidants, and these results are included for comparison.

2. Experimental

2.1. Höje River and Källby STP

The Höje River basin is located near the city of Lund (population 80,000) and reaches the Öresund nearby. The Källby STP is located by the Höje River just south of the city. The STP, consisting of bar screening, grit

removal, primary clarification, activated sludge, secondary sedimentation, chemical phosphorous removal and final sedimentation, discharges the treated sewage into the Höje River. The hydrology of the small Höje River basin has been investigated in several projects [19,20]. The total area of the Höje River basin is about 310 km^2 and the soil types are mainly sandy loam and moraine with inclusions of fine and coarse sediments. The land use is divided between agricultural (59%), forest (18%), urban (12%), meadows (10%) and lakes (<1%). The river sediment is composed mainly of clay minerals, quartz, and some feldspar, with an overall organic content less than 10% [19]. Based on data collected by the Swedish Meterological and Hydrological Institute (SMHI) during 1961–1990, the average annual precipitation for the Höje River basin is 666 mm and the average annual temperature is 7.9 °C. The river discharge is seasonally dependent and varies between 0.1 and 15.0 m^3/s with an annual average of 2.4 m^3/s. Exchange between the Höje River and the ground water is seasonally dependent with a net inflow of groundwater during the winter months and a net loss of water to the ground during the summer months [19].

The flow in Höje River is recorded on a daily basis by SMHI at the Trolleberg station situated about 280 m downstream from the point at which the Källby STP releases treated sewage into Höje River. Measurements at Trollberg capture 76% (237 km^2) of the natural runoff in the Höje River basin. The discharge from Källby STP is routinely measured by the staff at the plant. The monthly average flow in the Höje River and the effluent from the Källby STP in 2002 are illustrated in Fig. 1. The Källby STP discharge in the summer months commonly composes over 75% of the flow in the river with an inverse relationship during winter months. Källby is not the only STP discharge into Höje River; upstream STPs servicing roughly 22,000 people discharge approximately 0.07 m^3/s into the Höje River on an annual basis.

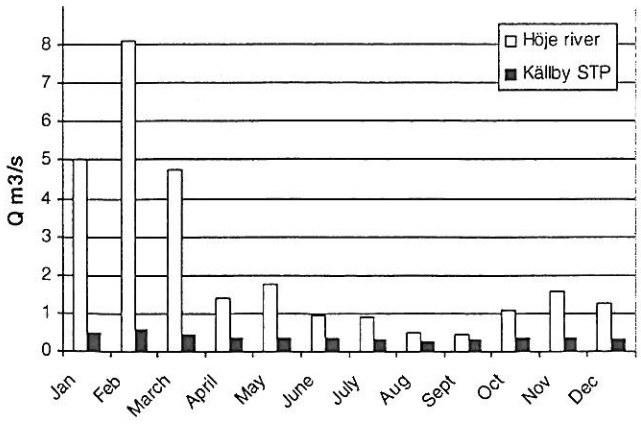

Fig. 1. Monthly average flow (m^3/s) in Höje River registered just downstream from Källby STP and the monthly average effluent (m^3/s) from Källby STP in 2002.

Table 1
Basic dam parameters

Parameter	Dam					
	1	2	3	4	5	6
Area (m^2)	5000	30000	10000	11000	16000	16000
Retention time (h)	4	24	8	9	13	13

Källby STP releases the sewage into Höje River through six excavated dams connected in series. The average depth of the dams is roughly 1 m. The hydraulic retention time in the treatment plant is 15–16 h. The total hydraulic retention time in the dams are approximately 71 h, and is distributed over the dam system as given in Table 1 [21].

During the particular day when the samples were collected, the flow in the Höje River at the Trolleberg station (downstream the Källby STP) was 0.9 m^3/s and the outflow from the STP into Höje River was 0.36 m^3/s. The consumption of drinking water in the area was registered at 0.28 m^3/s. The difference, 0.08 m^3/s, corresponds to the contribution from stormwater runoff into the sewage system [22]. All flow rates represent daily averages. A rough estimate (based on measurements of the average depth and width) of the retention time in the river reach from the effluent of dam 6 to the last sampling point 7543 m downstream is 5–10 h at a flow rate of about 0.9 m^3/s.

2.2. Sampling

The sampling campaign was carried out on October 21 in 2002. Samples were collected: (i) in the influent and the effluent of the STP, where the treated sewage is discharged into dam 1; (ii) at the effluent of dams 1, 2 and 6; and (iii) in the Höje River just upstream of the STP and downstream at 283, 4021 m, and at 7543 m from the effluent of dam 6. The last sampling point is located just before the Höje River flows into the harbor of the city of Lomma and the sea of Öresund (see Fig. 2). The black area on the map just northeast of dam 1 is the Källby STP.

To obtain a representative sample of the STP influent, an averaged sample was prepared by mixing flow proportional samples taken for every 1200 m^3 of sewage influent. The automatic sampling took place during a 24 h period, starting at 10:00 a.m. the 20th of October. A total sampling volume of approximately 7.0 l was collected in a plastic (polypropylene) container refrigerated during the sampling process.

The samples obtained from the dams and the river were collected during a 2 h period starting at 10:00, October 21. Two-litre bottles were used as sampling containers. The water samples were collected by lowering a bottle with the head pointing downward into the water, and, while keeping it under the water, slowly turning it with the head upwards and allowing it to fill completely before putting on the cap. The samples were then immediately brought to the laboratory and put in a freezer for later analysis.

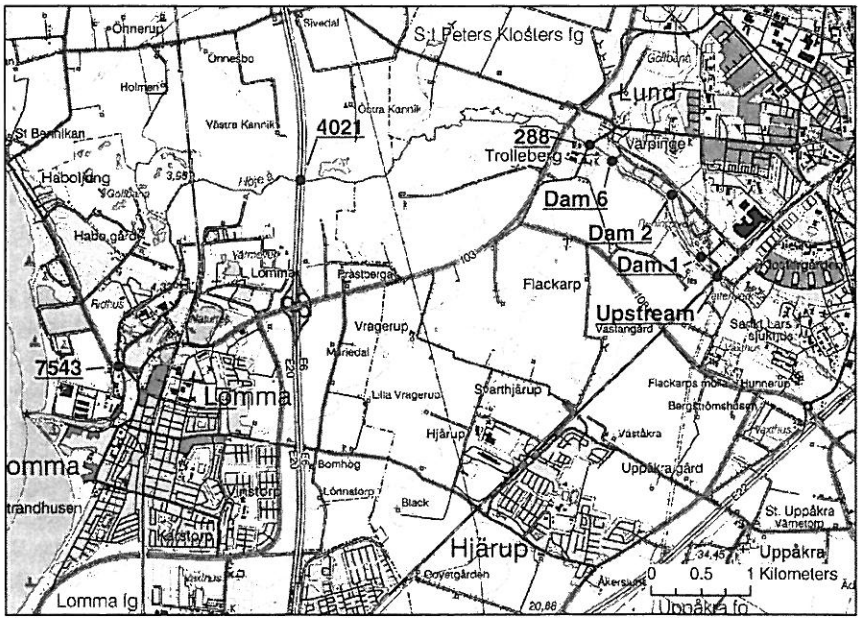

Fig. 2. Overview Höje River system and location of sampling points.

2.3. Analysis

2.3.1. Chemicals

The reference compounds (purity >97% by weight) were purchased from Sigma–Aldrich and Promochem Standard Supplies. The solvents and water were of gradient grade (Chromasolv, Riedel-de-Haen) or better. Formic acid (FA), HCl, triethyl amine (TEA) and other reagents used in this study were of pro analysi grade or better.

2.3.2. GC–MS analysis

Target analyses of triclosan and acidic drugs as their methyl derivatives were performed by GC–MS on GCQ Plus (ThermoFinnigan Inc., USA) equipped with an automatic sample injector A200S (CTC Analytics, Switzerland). The compounds were concentrated from 0.5 to 1 l water (pH < 3, added formic acid or HCl) using RP-C18 (6 ml, 1 g sorbent from IST Inc., UK or Phenomenex Inc., USA) and eluted with 10 ml acetone. Samples were previously centrifuged and filtered through 1.2 μm glass-fiber filter to avoid clogging on RP-C18. Methylation was performed using methyl chloroformate. Analysis of carbamazepine was performed in extracts before methylation. GC separation was performed on a 30 m × 0.25 mm i.d. column coated with 0.25 μm chemically bonded phase ZB-5 (Phenomenex, USA). Injector temperature was 240 °C operated on a splitless mode (split open time 2 min). The GC was programmed to maintain constant velocity of 35 cm/s of He with an initial temperature of 100 °C held in 11.5 min and then increased to 180 °C at 4 °C/min, 240 °C at 3 °C/min, 300 °C at 4 °C/min, and held at 300 °C for 5 min. The ion source temperature and the transfer line temperature were held at 180 °C and 275 °C, respectively. The MS data were collected in EI mode (full scan, *m/z* 80–470). A calibration (at least five points) with standard solutions was used for quantification of the analytes detected by their specific *m/z*. Excepted metabolites were of ibuprofen, galaxolide, BHT aldehyde and the degradation products of NP, and TIC was used to estimate their final concentrations.

2.3.3. LC–MS analysis

Basic pharmaceuticals and carbamazepine were extracted from 0.8 to 1.0 l water using Isolute (IST, Inc., UK) SPE cartridges (6 ml, 1 g mixed phase sorbent of C2/ENV+). Samples of wastewater were previously centrifuged and filtered through 1.2 μm glass-fiber filter to avoid clogging of sorbents. Analytes were eluted with 2× 5 ml methanol containing 2–5% TEA and then 2× 5 ml methanol containing 2–10% FA. After removal of the excess solvents the volume was brought to 1.5 ml with acidified (formic acid) ultra-pure grade water containing 5–20% methanol. The eluates were centrifuged and finally filtered through 0.45 μm glass-fiber filter. Chromatographic separation was performed as described elsewhere [27]. The mass-spectrometric detection was performed on LCQ-Duo (ThermoFinnigan Inc., USA) equipped with electrospray. MS/MS data were acquired in ESI+ mode (capillary temperature 230 °C; sheath and auxiliary nitrogen gas flows set to 60 and 20; source voltage 4.50 kV, source current 80.00 μA, capillary voltage 29 V). The collision energy required to produce the desired quantity of daughter ions in selective reaction monitoring (SRM) was individually optimized for each analyte. SRM detection was performed by monitoring daughter ions. A calibration (5–10 points) was performed using standard solutions in acidified ultra-pure water containing 5–10% methanol. Details concerning the procedures as well as

GC–MS and LC–MS analyses can be found elsewhere [12].

Separate samples where sent to a commercially accredited laboratory for analysis with respect to major elements and a selection of trace elements. Except from the elements that were used as natural tracers in this study, Cl^- and B, the results from the analyses are not reported herein.

3. Results

The sampling protocol described above provides "snapshots" of analyte concentrations at STP influent, effluent, and at various points downstream. As such, the investigation is intended as a preliminary foray into the general impacts of STP and natural processes on selected PhACs. These impacts are characterized in terms of removal efficiency (simple fraction of effluent to influent concentrations) across the Källby STP, and in terms of direct comparison of concentrations at selected downstream locations. We also consider data with dilution effects approximately removed by defining concentrations relative to that of passive tracers (Cl^- and B).

3.1. Occurrence in the influent and effluent and removal efficiency of the Källby STP

The results from the analyses of the samples collected in the influent and effluent of the Källby STP are presented in Table 2. The removal efficiencies were calculated and provided in the table together with data reported in other investigations. Removal efficiencies display a wide range with numerous species surviving treatment at greater than half their influent concentrations, including diclofenac, the anti-epileptic carbamazepine, a β-blocker (propanolol), and both antibiotics trimetoprim and sulfamethoxazole. Low removals

Table 2
Occurrence (μg/l) of investigated substances in the influent and effluent of the Källby STP and the removal efficiency of the plant

Therapeutic class	Substance	Källby STP in-	Källby STP out-	STP effluents survey [27]	Calculated removal efficiency	Removal efficiencies [1,12,23,24,32,33]
Lipid-regulators	Clofibric acid	n.f.	n.f.			
	Gemfibrozil	0.71	0.18	0.84–4.76	75%	69%
NSAIDs	Ibuprofen	3.59	0.15	0.05–7.11	96%	90%
	Flurbiprofen	n.f.	n.f.			
	Fenoprofen	n.f.	n.f.			
	Ketoprofen	0.94	0.33	n.d–1.62	65%	69% (2)
	Naproxen	3.65	0.25	1.12–5.22	93%	66%
	Diclofenac	0.16	0.12	0.68–5.45	22%	17–69%
	Indometacin	n.f.	n.f.			
Anti-epileptic β-blockers	Carbamazepine	1.68	1.18	0.87–1.2	30%	7%
	Atenolol	0.03	0.16		(1)	
	Metoprolol	0.16	0.19	0.08–0.39	(1)	83%
	Propanolol	0.05	0.03	0.01–0.09	32%	96%
Antibiotics	Trimetoprim	0.08	0.04	0.04–0.13	49%	
	Sulfamethoxazole	0.02	0.07	0.05–0.09	(1)	
Metabolites	Hydroxy-ibuprofen	0.99	0.05		95%	
	Carboxy-ibuprofen	10.75	0.43		96%	96–99.9%
Usage/origin						
Biocide	Triclosan	0.38	0.16		58%	55–95%
Flame-retardant	Tris(2-chloro-isopropyl)phosphate	2.79	2.26		19%	
Antifoam, hydraulic liquid, additive, etc.	Tris(2-butoxyethyl)phosphate	9.44	1.89		80%	
Antioxidant	BHT	2.53	0.61		76%	
Oxidation product of BHT	BHT-aldehyde	0.56	0.49		12%	
Synthetic musk (odorant)	Galaxolide(HHCB)	0.79	1.08		(1)	
Degradation product of surfactant NP-ethoxylate	Nonyl phenol (NP)	1.14	0.34		71%	
Soap component (surfactant)	Palmitic (hexadecanoic) acid	35.91	0.71		98%	
Soap component (surfactant)	Stearic (octadecanoic) acid	41.00	0.80		98%	
Component in soft drinks	Caffeine	3.69	0.22		94%	>99%
Plasticizer	DEP	0.19	0.02		89%	
Plasticizer	DIBP	0.04	0.01		65%	
Plasticizer	DBP	0.15	0.03		83%	
Plasticizer	DEHP	0.27	0.02		94%	

Data reported in other investigations are given for comparison. Remark: n.f.: not found; (1) concentration in effluent larger than concentration in influent; (2) an activated sludge treatment step was used. A lower efficiency (48%) was encountered when a biological filter was used.

were also implied for Tris(2-chloroisopropyl)phosphate (flame retardant), BHT-aldehyde (oxidation product of BHT) and synthetic musk (HHCB). Clofibric acid, flurbiprofen, ketoprofen and indometacin were not detected in this study. Clofibric acid and flurbiprofen were not expected to be found but were included due to the proximity of Höje River basin to the European continent.

Ibuprofen is one of the dominating PhACs found in sewage. Ibuprofen and also the basic metabolites of ibuprofen, hydroxy-ibuprofen and carboxy-ibuprofen, have been reported to be easy to eliminate during sewage treatment [23]. This is confirmed in the present study with a removal efficiency of 95–96%. A different finding was made by Stumpf et al. [24], who reported hydroxy-ibuprofen to escape the treatment plant without being degraded. Specific operational parameters of the activated sludge process were, however, found to be crucial for the removal of hydroxy-ibuprofen [12].

3.2. Mass balance

Following the principles in the environmental risk assessment for new human pharmaceuticals proposed for the EU [18,25], a mass balance calculation was carried out and theoretical concentrations of the selected substances in the influent to Källby STP were determined.

The statistical unit at the Swedish Pharmaceutical Company (Apoteksbolaget) provided data on the amount of drugs that were sold in the region of Skania (1,145,000 inhabitants) where Lund is the second largest city. A rough theoretical estimate of the PhACs in the influent to the STP were calculated based on the per capita consumption rate (in the region of Scania) multiplied by the population of Lund (79,000) coupled with literature values of percentages that are excreted. The results from the calculation are presented in Table 3 together with the measured concentration in the influent to the STP. Significantly lower concentrations of gemfibrozil, trimetoprim and atenolol and significantly higher concentrations of carbamazepin were measured compared to the theoretical values. The measured and theoretical concentrations for diclofenac, naproxen and metoprolol are of the same magnitude.

3.3. Occurrence and fate in dam and in Höje River system

The concentration of the selected substances (presented earlier in Table 2) in the dam system and in Höje River, upstream and downstream of the STP outfall, are summarized in Table 4 together with data reported in the literature for comparison.

The concentrations observed in this study are similar in magnitude to other investigations reported in the literature (e.g., [2,4]). Ibuprofen, atenolol and metoprolol were found in the sample that was taken upstream from the STP outfall and are believed to originate from the small treatment plants located upstream. The data presented in Table 4 represent a snapshot in time of the distribution of substances along the dam and river system. The concentrations of chloride (Cl^-) and boron (B) were used as natural inert tracers to estimate the relative extent of dilution of PhACs measured in the effluent of the STP on concentrations measured further downstream. Both compounds are abundant in sewage and at greater concentrations than background concentrations in Höje River (as measured just upstream from the STP outfall). Additional sources of chloride in the river principally occur from de-icing practices during wintertime [19]. Natural background concentrations of boron in the Swedish environment (natural waters and soil) are extremely low.

Under the assumption of steady state, the accumulative dilution of Cl^- and B at each sampling point along the course from the STP effluent to Lomma harbor was calculated (Fig. 3).

The mass in the aqueous phase is constant and the dilution factor between two sampling points is calculated by taking the ratio of the concentration in the actual sampling point and the concentration in the previous sampling point (starting at the effluent from the STP). When calculating the dilution between the effluent of dam 6 and the point in Höje River 283 m downstream, the background concentration in Höje River was taken into account. The accumulated dilution up to a certain point was simply calculated by multiplying the precedent dilution factors. If the calculated cumulative dilution suddenly increases, water is either abstracted from the system by evaporation, and thus concentrating the solutes,

Table 3
Comparison between the theoretical and measured concentrations of PhACs in the influent to the Källby STP

Substance	Excretion	Theoretical concentration (μg/l)	Measured concentration (ug/l)	Reference excretion
Gemfibrozil	50% (as glucorinide)	3.25	0.71	[32]
Diclofenac	15% unchanged, <1% as conjugates	0.32	0.16	[32]
Ibuprofen	1–8% as unchanged, 14% as glucuronide	0.46–3.66	3.59	[32,34]
Naproxen	65% as acyl-glucoronide	5.72	3.65	[34]
Ketoprofen	>80% as acyl-glucuronide	–	0.94	[34]
Propranolol	<1% (unchanged)	0.01	0.05	[32]
Metoprolol	3–10%	0.18–0.59	0.16	[32]
Atenolol	90%	3.38	0.03	[35]
Trimetoprim	60%	0.37	0.08	[36]
Sulfametoxazol	15% (unchanged)		0.02	[36]
Carbamazepin	1–2% (unchanged)	0.11	1.68	[32]

Table 4
Concentration (μg/l) of selected PhACs and other substances at the effluent of the STP where the treated sewage is discharged into dam 1; at the effluent of dams 1, 2 and 6; and in the Höje River just upstream of the STP and downstream at 283, 4021 m, and at 7543 m from the effluent of dam 6

Substance	Maximum (med)	Reference	STP out	1	2	6	Upstream	283	4021	7543
Gemfibrozil	0.51 (0.052)	[32]	0.18	0.26	0.23	0.18	<0.001	0.17	0.07	0.001
Ibuprofen	0.53 (0.07)	[32]	0.15	0.78	0.52	0.64	0.01	0.22	0.08	0.11
Ketoprofen	0.12	[32]	0.33	0.29	0.23	0.08	n.f.	0.07	0.02	0.01
Naproxen	0.39 (0.07)	[32]	0.25	0.85	0.76	0.67	n.f.	0.25	0.09	0.11
Diclofenac	1.20 (0.15)	[32]	0.12	0.17	0.18	0.14	n.f.	0.12	0.01	n.f.
Carbamazepin	1.1 (0.25)	[32]	1.18	0.41	0.37	0.74	<0.001	0.5	0.45	0.1
Atenolol	0.241 (0.016)	[18]	0.16	0.28	0.22	0.26	0.03	0.01	0.01	0.06
Metoprolol	2.2 (0.045)	[32]	0.19	0.18	0.16	0.24	0.03	0.06	0.07	0.06
Propranolol	0.59 (0.012)	[32]	0.03	0.02	0.02	0.05	<0.001	0.01	0.01	0.01
Trimetoprim	0.20	[36]	0.04	0.04	0.04	0.04	<0.001	0.02	0.02	0.01
Sulfamethoxazole	0.48 (0.03)	[36]	0.07	0.05	0.05	0.02	<0.001	0	0	0.01
Hydroxi-ibuprofen			0.05	0.38	0.28	0.32	<0.001	0.06	0.02	0.05
Carboxy-ibuprofen			0.43	4.09	2.73	2.39	<0.001	0.68	0.23	0.29
Triclosan			0.16	0.19	0.16	0.11	n.f.	0.07	0.02	n.f.
Tris(2-chloro-isopropyl)phosphate			2.26	7.02	6.76	2.7	<0.2	1.13	0.54	0.5
Tris(2-butoxyethyl)phosphate			1.89	9.63	5.3	2.7	<0.001	1.21	0.63	0.46
BHT			0.61	0.44	0.32	0.57	0.62	0.47	0.16	0.1
BHT-aldehyde			0.49	0.17	0.14	0.44	0.16	0.84	0.28	0.11
Galaxolide(HHCB)			1.08	1.58	1.6	0.65	0.03	0.23	0.15	0.13
Nonyl phenol (NP)			0.34	1.12	0.88	0.26	0.05	0.2	0.12	0.04
Palmitic (hexadecanoic) acid			0.71	7.97	3.62	1.17	0.72	0.62	0.43	0.78
Stearic (octadecanoic) acid			0.8	7.9	4.49	1.7	1.15	0.84	0.55	1.17
Caffeine			0.22	0.43	0.07	0.38	<0.005	0.11	0.01	0.01
DEP			0.02	0.19	0.13	0.06	0.04	0.03	0.01	0.03
DIBP			0.01	0.07	0.06	0.02	0.06	0.01	0.01	0.02
DBP			0.03	0.06	0.05	0.05	0.08	0.06	0.02	0.05
DEHP			0.02	0.13	0.09	0.03	0.09	0.03	0.01	0.04

Data reported in other investigations are given for comparison. Remark: n.f.: not found (concentration < 1E−4 μg/l).

or mass is returning to the water phase from reservoirs by desorption or dissolution.

The calculated cumulative dilution based on the boron and chloride data are consistent. But due to minor spuriousity in the boron data, the chloride data were used to model the cumulative dilution of the dam and Höje River systems. As seen in Fig. 3, the release of the sewage into Höje River had a large affect on the cumulative dilution, with a value of 0.26 at 283 m downstream, and no additional dilution further downstream. Sampling took place at the end of a dry summer when the river flow was very low and there was likely to be a net loss of water from the river to the groundwater system.

PhAC values presented in Table 4 were recalculated (Figs. 4–7) to represent a hypothetical situation with no dilution. For this data, any decreasing trend along the river reach for a certain substance may therefore be attributed to abiotic or biotic transformation reactions, volatility or physical sequestration.

The concentrations of the NSAIDs increased from the STP effluent to dam 1, possibly reflecting a transient desorption or other release from temporary sequestration, after which it appeared roughly constant in the dam system and down to the first sampling point in the river at 283 m. During the next 4 km, the concentrations of all four species declined significantly, reflecting transformation and/or sequestration processes.

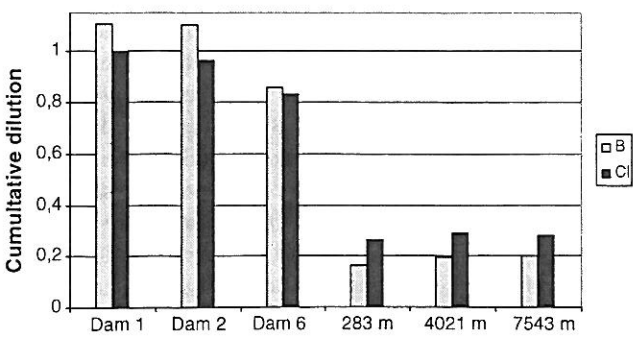

Fig. 3. Cumulative dilution in the dam and Höje River system.

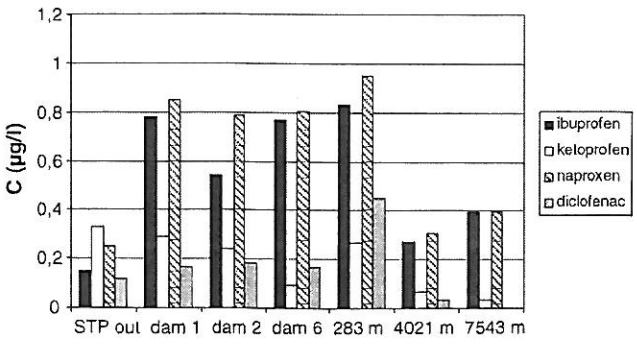

Fig. 4. Concentrations of the NSAIDs ibuprofen, ketoprofen, naproxen and diclofenac in the STP effluent and in the dam and river system. Note that the data has been recalculated to reflect a hypothetical scenario with no dilution.

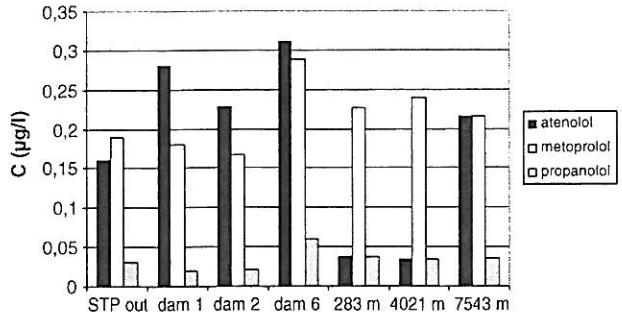

Fig. 5. Concentrations of the β-blockers—atenolol, metoprolol and propanolol in the STP effluent and in the dam and river system. Note that the data has been recalculated to reflect a hypothetical scenario with no dilution.

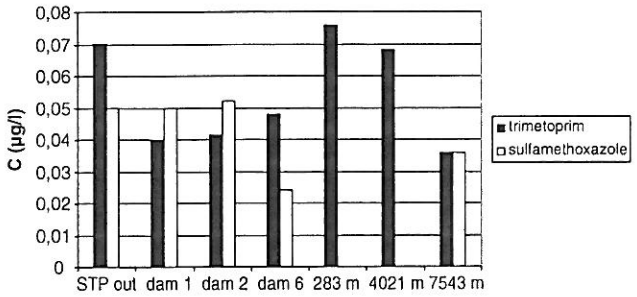

Fig. 6. Concentrations of the antibiotics trimetoprim and sulfamethoxazole in the STP effluent and in the dam and river system. Note that the data has been recalculated to reflect a hypothetical scenario with no dilution.

The concentration of metoprolol, propanolol and trimetoprim, remained unchanged, for the most part, in the dam and river system. The concentrations of atenolol, sulfamethoxazole, carbamazepine and gemfibrozil show a larger spatial variation. Small variations in the concentration at different sample locations are attributed to spatial and temporal noise reflecting roughly a 10–15% coefficient of variation between sample locations for a given compound; this type of variation is common in analyte concentrations in multiple grab samples over a short time interval from a single location. Contrary to other PhACs in this study, atenolol and metropolol (0.03 µg/l) were detected in the river just upstream of the Källby STP outfall, likely a result of the upstream STPs.

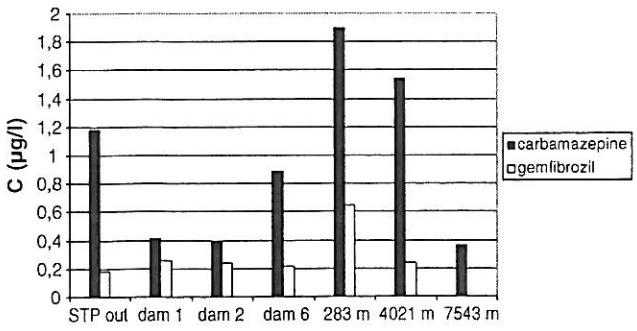

Fig. 7. Concentrations of carbamazepine och gemfibrozil in the STP effluent and in the dam and river system. Note that the data has been recalculated to reflect a hypothetical scenario with no dilution.

4. Discussion

The data presented herein represent only a snapshot in time of the occurrence of PhACs in the influent and effluent of the Källby STP and at selected downstream locations from the point of discharge. The theoretical (predicted) concentrations of PhACs from the mass balance calculations are a gross approximation of the actual load on the Källby STP, and by factoring the removal efficiency of the plant, the eventual load on lower Höje River basin. While rather good agreement was found between the theoretical and actual concentrations of ibuprofen, diclofenac, naproxen and metoprolol, significant differences were observed for gemfibrozil, trimetroprim, atenolol, and carbamazepin. Discrepancies between measured and theoretical values could be associated with seasonal variations in annual consumption rates. In addition, variations in excretion rates, strongly affected by an individual's sex, age, hypoxaemia, nutrition, and thyroid function [26], among other factors, further confound comparison. According to the figures presented in Table 3, the substances with a high metabolic rate in humans (low excretion rate as parent compound) are ibuprofen, diclofenac, propranolol, metoprolol, and carbamazepine. These substances exhibit half-lives of less than 1–2 days depending on external factors (e.g., temperature and radiation) [23,27]. Atenolol, naproxen, trimetoprim are substances with a low metabolic rate in humans; they are excreted mainly unchanged or as acyl-glucuronide (naproxen), and have documented half-lives in the environment ranging from 10 days to 1 year [28].

The limited quantity of data is used below to infer the relative degree of persistence based on spatial trends. Additional studies will be required to provide definitive confirmation of many of the discussion points. Spatial variations in the concentration of PhACs (recalculated to reflect a hypothetical scenario without dilution) in Höje River likely do not represent temporal fluctuations in the mass flux from the STP; the dam system substantially dampens variations in flow rate from the STP. In addition, the retention time in the river (from the effluent at dam 6 down to sampling point at 7543) is roughly 10% of the total retention time in the dam system.

The spatial concentrations of selected NSAIDs (ibuprofen, ketoprofen, naproxen and diclofenac) exhibit a significant decline along the Höje River (Fig. 4). All substances show a coherent behavior and support the idea that a high metabolic rate in humans is congruent with a short lifetime in aquatic environments. The exact mechanisms (e.g., abiotic degradation induced by solar irradiation, biotransformations and physical sequestration) responsible for this decline are unknown. A contribution of the oxidative metabolic pathway to hydroxy- and carboxy-derivatives may play an important role for the removal of ibuprofen while other mechanisms are probably also responsible for the removal of naproxen and diclofenac, such as physical sequestration. The log K_{ow} (octanol–water) values of naproxen (1.7) and diclofenac (1.12) are still relatively high even at pH 7.4 [29] to exhibit affinity for organic matter in the sediments according to classic theory.

The antibiotic trimetoprim, with a $\log K_{ow}$ of 0.91, and sulfametoxazole, with a $\log K_{ow}$ value of 0.89 demonstrate an expected high degree of persistence in the aqueous environment (Fig. 6); their individual life half times are reported [13,28] to be the order of 20–100 days and over 1 year, respectively.

However, the spatial trends of the β-blockers (Fig. 5) reveal that a high metabolic rate in humans does not necessarily induce a short lifetime in aquatic environments receiving a constant mass loading. Both propanolol and metoprolol show a high degree of persistence in the aquatic environment, although they exhibit a high metabolic rate in humans. Assuming a high metabolic rate is congruent with the rate of environmental degradation, and accounting for solubility through the distribution coefficient, the concentration of metroprolol ($\log K_{ow}$ values of 1.88 [29]) and propanolol ($\log K_{ow}$ value of 3.48 [31]) would be expected to decline in the river system, yet their concentrations remain fairly constant. In contrast, the concentration of atenolol ($\log K_{ow}$ values of 0.23 [30]) would be expected to remain fairly constant, yet declined.

In addition, carbamazepine, which is metabolized to a very high degree in humans and has a $\log K_{ow}$ value of 2.45, also shows a high degree of persistence in the aquatic environment. The concentration (recalculated to reflect a hypothetical scenario with no dilution) of carbamazepine increased dramatically, up to above 2 μg/l, through the dam system up to the sampling point at 283 m, and then steadily declined in the river system to a value below 0.4 μg/l at the last measuring point (7543 m). This spatial variation of carbamazepine and its persistence in aquatic environment may be attributed to the excretion of glucuronides which may act as a reservoir from which a later yield of the parent substance can occur. Gemfibrozil also exhibit the same spatial trend and is mainly (50%) excreted as glucuronide [32].

5. Conclusions

Removal efficiencies were calculated in the STP and found to display a wide range with numerous species surviving treatment at greater than half their influent concentrations, including diclofenac, the anti-epileptic carbamazepine, a β-blocker (propanolol), and antibiotics trimetoprim and sulfamethoxazole. Low removals were also observed for Tris(2-chloroisopropyl)phosphate (flame retardant), BHT-aldehyde (oxidation product of BHT) and synthetic musk (HHCB).

A theory consistent with the observations of this study is that the loading rate of PhACs relative to the collective rates of transformation govern persistence in the environment, regardless of the metabolic rates in humans. In the Höje River system, the rate of mass flux of NSAIDs is likely less than the collective rates of transformation; conversely, the loading rate of the β-blockers is greater than the rates of transformation. Development of a mechanistic understanding of environmental transformations and associated rates is paramount in understanding the true mechanism influencing persistence. In the interim, we cannot conclude per capita consumption of pharmaceuticals coupled with human metabolic rates is indicative of aquatic concentrations in receiving waters.

Acknowledgements

This study was partly supported by the Swedish Geotechnical Institute (SGI) Research Fund and partly by the Commission of the European Communities under Grant No. EVK1-CT-2000-00048. Ingemar Dellien, Christer Jonasson and Mikael Petterson at the Technical Services Department at Lund Water and Sewage Works, Sweden, are acknowledged for providing information of the Källby STP and helping out in all possible ways. Hakan Basagaoglu (Idaho National Engineering and Environmental Laboratory), Lennart Larsson (SGI) and Karsten Håkansson (SGI) contributed in the early planning of this project.

References

[1] T. Heberer, Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data, Toxicol. Lett. 131 (2002) 5–17.
[2] C.G. Daughton, T.A. Ternes, PPCPs in the environment: agents of subtle change, Environ. Health Perspect. 107 (1999) 907–944.
[3] B. Halling-Sørensen, S.N. Nielsen, P.F. Lanzky, F. Igerslev, H.C. Lutzhoft, S.E. Jørgensen, Occurrence, fate, and effects of pharmaceutical substances in the environment—a review, Chemosphere 36 (1998) 357–393.
[4] D.W. Kolpin, E.T. Furlong, M.T. Meyer, S.D. Zaugg, L.B. Barber, H.T. Buxton, Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance, Environ. Sci. Technol. 36 (2002) 1202–1211.
[5] K. Kümmerer (Ed.), Pharmaceuticals in the environment—sources, fate, effects and risks, Springer-Verlag, Berlin, 2001.
[6] M. Ahel, A. Jelicic, Occurrence of analgetics in a municipal solid waste landfill and adjacent groundwater aquifier, In: S. Matsui (Ed.), Proceedings of the Third IWA Specialized Conference on Hazard Assessment and Control of Environmental Contaminants –ECOHAZARD'99, Otsu, Japan, 1999, pp. 497–504.
[7] J.V. Holm, K. Rugge, P.L. Bjerg, T.H. Christensen, Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grinsted, Denmark), Environ. Sci. Technol. 29 (1995) 1415–1420.
[8] N. Paxéus, Organic compounds in municipal landfill leachates, Water Sci. Technol. 42 (2000) 323–333.
[9] D.M. Fry, C.K. Toone, DDT-induced feminization of gull embryos, Science 231 (1981) 919–924.
[10] S.A. Snyder, P. Westerhoff, Y. Yoon, D.L. Sedlak, Pharmaceuticals, personal care products and endocrine disrupters in water: implications for water industry, Environ. Eng. Sci. 20 (5) (2003) 449–469.
[11] S.-E. Jørgensen, B. Halling-Sørensen, Drugs in the environment, Chemosphere 40 (2000) 691–699.
[12] N. Paxéus, Removal of Selected NSAIDs, Gemfibrozil, Carbamazepine, β-blockers, trimethoprim and triclosan in conventional wastewater treatment plants in five EU countries and their discharge to the aquatic environment, Water Sci. Technol. 50 (5) (2004) 253–260.
[13] H. Hektoen, J.A. Berge, V. Hormazabal, M. Yndestad, Persistence of antibacterial agents in marine sediments, Aquaculture 133 (1995) 175–184.

[14] M. Rabolle, N.H. Spliid, Sorption and mobility of metronidazole, olaquindox, oxytetracycline and tylosin in soil, Chemosphere 40 (2000) 715–722.
[15] R.L. Yeager, B.A. Halley, Sorption/desorption of 14C[efromycin] with soils, J. Agric. Food Chem. 38 (1990) 883–886.
[16] J. Tolls, Sorption of veterinary pharmaceuticals in soils: a review, Environ. Sci. Technol. 35 (2001) 3397–3406.
[17] T. Scheytt, P. Mersmann, T. Heberer, Natural attenuation of pharmaceuticals, in: Proceeding of the Second International Conference on Pharamceuticals and Endocrine Disrupting Chemicals in Water, October 9–11, Minneapolis, MN, 2001, pp. 253–259.
[18] D. Calamari, E. Zuccato, S. Castiglioni, R. Bagnati, R. Fanelli, Strategic survey of therapeutic drugs in the rivers Po and Lambro in Northern Italy, Environ. Sci. Technol. 37 (2003) 1241–1248.
[19] R. Berndtsson, Transport and sedimentation of pollutants in a river reach: a chemical mass balance approach, Water Resour. Res. 26 (1) (1990) 549–1558.
[20] J. Niemczynowicz, An investigation of the areal and dynamic properties of rainfall and its influence on rainfall generating processes, Report 1005, Department of Water Resources Engineering, Lund University, Lund, Sweden, 1984.
[21] I. Dellien, The technical services department at Lund water and sewage works, Sweden, 2003, Personal communication.
[22] C. Jonasson, The technical services department at Lund water and sewage works, Sweden, 2003, Personal communication.
[23] H.-R. Buser, T. Poiger, M.D. Muller, Occurrence and environmental behaviour of the chiral pharmaceutical drug Ibuprofen in surface waters and in waste waters, Environ. Sci. Technol. 33 (1999) 2529–2535.
[24] M. Stumpf, T.A. Ternes, K. Haberer, W. Baumann, Isolation of ibuprofen-metabolites and their importance as pollutants of the aquatic environment, Vom Wasser 91 (1998) 291–303.
[25] J.O. Straub, Environmental risk assessment for human pharmaceuticals in the European Union according to the draft guideline/disscussion paper of January, Toxicol. Lett. 131 (2002) 137–143.
[26] Gr. Park, Drug metabolism, Br. J. Anaesth. CEPD Rev. 1 (2001) 185–188.
[27] R. Andreozzi, R. Marotta, N. Paxéus, Pharmaceuticals in STP effuents and their solar photodegradation in aquatic environment, Chemosphere 50 (2002) 1319–1330.
[28] M.L. Richardson, J. Brown, The fate of pharmaceuticals in the aquatic environment, J. Pharm. Pharmacol. 37 (1985) 1–12.
[29] SRC PhysProp (2001), accessed via http://esc.syrres.com/interkow/physdemo.htm.
[30] http://www.rxlist.com.
[31] A. Adveef, C.M. Berger, C. Brownell, pH-Metric solubility. Part 2: Correlation between the acid-base titration and the saturation shake-flask solubility–pH methods, Pharm. Res. 17 (2000) 85–89.
[32] T.A. Ternes, Occurrence of drugs in German sewage treatment plants and rivers, Water Res. 32 (1998) 3245–3260.
[33] D. Sabaliunas, S.F. Webb, A. Hauk, M. Jacob, W.S. Eckhoff, Environmental fate of triclosan in the river Aire basin, UK, Water Res. 37 (2003) 3145–3154.
[34] J. DeRuiter, Non-steroidal antiinflammatory drugs (NSAIDs), Princ. Drug Action 2 (2000) 1–23.
[35] E. Zuccato, D. Calamari, M. Natangelo, R. Fanelli, Presence of therapeutic drugs in the environment, Lancet 355 (2000) 1789–1790.
[36] R. Hirsch, T. Ternes, K. Haberer, K.-L. Kratz, Occurence of antibiotics in the environment, Sci. Total Environ. 225 (1999) 109–118.