

# Results from the Swedish screening 2006

## Sub report 4: Pharmaceuticals

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## Summary

As an assignment from the Swedish Environmental Protection Agency, IVL has during 2006/2007 performed a "Screening Study" of pharmaceuticals. The overall objectives of the screening were to determine the concentrations of the selected substances in a variety of media in the Swedish environment, to highlight important transport pathways, and to assess the possibility of current emissions in Sweden.

Pharmaceuticals are frequently spread by domestic use and the screening programme was thus focused on sewage treatment plants and landfills. The importance of diffusive spreading of the pharmaceuticals in an urban area was further investigated in the Stockholm area where water, sediment and biota samples were collected. Environmental background levels in water and sediment were determined in samples from three background lakes where the influence from human activities was considered minor. The number of samples are listed in the table below.

	Surface Water	Sediment	Sewage Water	Leachate Water	Sludge	Biota	Total
Regional	9	-	42	2	19	-	72
National	9	9	12	3	14	9	56
Total	18	9	54	5	33	9	128

All pharmaceuticals included in this screening study purposely affect the human nervous system, having the ATC-main code 'N'. In 2006 the Swedish consumption of drugs of this therapeutic use was 825 million Defined Daily Doses corresponding to a net cost of 6 104 million SEK. The central nervous system (CNS) represents the largest part of the nervous system, including the brain and the spinal cord. Together with the peripheral nervous system, it has a fundamental role in the control of behaviour. The basic pattern of the CNS is highly conserved throughout the different species of vertebrates and during evolution.

Pharmaceuticals included in this screening study were; analgetics (fentanyl, dextropropoxyphene), anesthetics (propofol), dopaminergic agonists (bromokriptine), neuroleptics (thioridazine), dibenzoxazepines (clozapine), benzodiazepines (flunitrazepam, diazepam and oxazepam), anti-psychotics (risperidone), sedatives (zolpidem) and selective serotonin re-uptake inhibitors, SSRIs (sertraline, fluoxetine, citalopram and paroxetine).

Oxazepam was the most frequently detected substance in water as well as the substance being found in the highest concentrations in sewage water samples. Furthermore, it was the only substance being detected in surface water samples. This can not entirely be explained by its sales volume (640 kg). Another factor that has to be considered is the tendency for other benzodiazepines to metabolise into this substance. Oxazepam has a rather low log Kow of 2.2 but was nevertheless also detected STP sludge.

Risperidone is sold in minor quantities in Sweden (8-20 kg) but is still detected in both influent and effluent waters. However, despite having a log Kow of 3.49, risperidone was still not detected in sludge. Among the three substances with the highest sales volumes, sertraline, dextropropoxyphene and citalopram, only citalopram could be detected in the sewage water samples. None of the

substances were detected in surface water. Thus, no clear correlation between sales volumes and concentrations in sewage water was identified in this study.

Factors such as degradation and the tendency to adsorb to sludge seem to influence the fate of the substances but no clear correlation between lipofilarity and the tendency to end up in sewage effluent can be drawn from these results. Factors such as the adsorption to solid matter; chelation, ionic interaction and chemisorption must also be considered to get a better understanding of the partitioning behaviour of pharmaceuticals.

Considering both aqueous and solid matrices citalopram is the most frequently encountered pharmaceutical. Sertraline was however found in the highest concentrations in sludge and also has one of the highest log Kow (5.29) among the pharmaceuticals in this study. Citalopram, with a log Kow of 3.74, was also frequently found in sludge while dextropropoxyphene, with a log Kow of 4.18, was only detected once in sludge and then in a concentration close to the detection limit. Citalopram was detected in several sediment samples while sertraline was only detected in one sediment sample.

Among the metabolites, zopiclone-n-oxide (metabolite of zopiclone), 7-aminoflunitrazepam (metabolite of flunitrazepam) and nordiazepam (metabolite of diazepam) were detected in water samples. Norfentanyl (metabolite of fentanyl) was detected in sludge.

Caffeine was introduced to the sampling scheme as an indicator for human influence. Caffeine was subsequently found in all environmental water samples where pharmaceuticals were detected. In the background lake Lilla Öresjön, where no pharmaceutical residues were expected to be found, the substance flunitrazepam along with caffeine was detected indicating a release of sewage water from houses not affiliated to any municipal sewage treatment plant.

Another marker for anthropogenic sources applicable when investigating pharmaceuticals is hydroxyl ibuprofen (metabolite of ibuprofen). Hydroxy ibuprofen was detected in all STP influent water samples and was also frequently encountered in the effluent water samples. Both caffeine- and hydroxy ibuprofen concentrations in influent water showed a slight correlation with the corresponding citalopram- and oxazepam concentrations.

## Sammanfattning

På uppdrag av Naturvårdsverket har IVL under 2006/2007 utfört en screening av läkemedel. I denna screening ingick såväl mätningar inom ett nationellt program som analys av prover som samlats in regionalt via länsstyrelserna.

Målsättningen med screeningen var att bestämma förekomst av utvalda läkemedelssubstanser i olika matriser i den svenska miljön, att identifiera viktiga transportvägar samt att få en uppfattning om pågående emissioner till den svenska miljön.

Läkemedel sprids framförallt via användning på sjukhus eller i hemmen samt från dess upplagring som avfall på deponier. Screeningen fokuserade därmed på reningsverk och deponier. Betydelsen av diffus spridning i urban miljö undersöktes ytterligare via provtagning av vatten, sediment och biota i centrala Stockholm. Bakgrundsnivåer av ämnena bestämdes i vatten och sedimentprover från lokaler där den humana påverkan ansågs vara marginell. För att få en uppfattning om detekterade koncentrationer kommer ifrån hushållsanvändning via avloppsströmmar analyserades även koffein, en vanligt förekommande substans i vatten från reningsverk. Antalet prover frångår av nedanstående tabell.

Program	Yt- vatten	Sediment	Avlopps- vatten	Lak- vatten	Slam	Biota	Total
Regional	9	-	42	2	19	-	72
Nationell	9	9	12	3	14	9	56
Total	18	9	54	5	33	9	128

Alla läkemedel som inkluderats i denna screening har terapeutiska effekter på nervsystemet och tillhör ATC-grupp "N". Under 2006 var den svenska användningen av denna grupp läkemedel 825 miljoner dygnsdoser till en kostnad av 6 140 MSEK. Centrala nervsystemet representerar den största delen av nervsystemet inklusive hjärna och ryggmärg. Tillsammans med det perifera nervsystemet har det en fundamental roll för kontroll över t ex beteende. Funktion och specifik lokalisering av nervsystemet återfinns i alla vertebrater och har i många avseenden bevarats genom evolutionen. Detta indikerar att dessa läkemedel har en potential att även påverka de akvatiska arter som har en receptoruppsättning liknande vår egen (främst groddjur och fisk).

De läkemedel som inkluderades i denna screening var; analgetika (fentanyl, dextropropoxyfen), anestetika (propofol), dopaminagonister (bromokriptin), neuroleptika (thioridazin), dibenzoxazepiner (klozapin), benzodiazepiner (flunitrazepam, diazepam och oxazepam), övriga lugnande (risperidon), lugnande (zolpidem) and selektiva sereotonineåterupptagshämmare, SSRI (sertralín, fluoxetin, citalopram och paroxetin).

Resultaten finns sammanställda i Tabell A och Tabell B där koncentrationsintervall för samtliga prover och matriser visas. I Tabell C redovisas halter av läkemedlen i vatten och slam från avloppsreningsverk uppdelade per län.

Oxazepam var det mest frekvent detekterade läkemedlet i vatten och även det läkemedel som uppmättes i högst koncentration i avloppsvattenprover (se Figur A). Ämnet detekterades även i

ytvatten. Den höga detektionsfrekvensen för oxazepam kan inte helt förklaras av försäljningsvolymen (ca 640 kg, 2006). Det faktum att oxazepam även utgör metabolit för andra läkemedel av bensodiazepin-typ bör beaktas. Trots att oxazepam har ett relativt lågt log Kow-värde detekteras ämnet också ofta i slamprover ifrån reningsverk.

Om resultaten ifrån både vatten- och fasta prover beaktas, är citalopram det ämne som detekteras mest frekvent. I slam är sertralin det läkemedel som påvisas i de högsta halterna. Detta förefaller rimligt då sertralin har ett mycket högt log Kow-värde, 5.29. Citalopram (log Kow; 3.74) kan också ofta påvisas i slam emedan dextropropoxifen (log Kow; 4.18) endast detekteras i låg halt i ett slamprov. Citalopram påvisas ofta i sediment emedan sertralin endast kan påvisas i ett sedimentprov.

Risperidon säljs endast i mindre kvantiteter i Sverige (ca 8-20 kg, 2006), men ämnet detekteras trots det ofta i avloppsvatten. Risperidon har ett högre log Kow-värde än oxazepam men detekteras trots detta inte i reningsverksslam. Av de tre läkemedlen med högst försäljningsvolym i studien; sertralin, dextropropoxifen och citalopram, detekteras endast citalopram i reningsverksslam. Ingen av dessa ämnen kunde detekteras i ytvatten. Studien visar således inte på någon säker korrelation mellan ett läkemedels försäljningsvolym och dess förekomst i avloppsvatten eller slam.

Av metaboliter detekterades zopiclon-n-oxid (metabolit av zopiclon), 7-aminoflunitrazepam (metabolit av flunitrazepam) och nordiazepam (metabolit av diazepam) i vatten. Norfentanyl (metabolit av fentanyl) detekterades i slam.

Faktorer såsom nedbrytningshastighet och benägenheten för läkemedelssubstansen att adsorberas till slampartiklar påverkar således vilken matris ämnet tenderar att hamna i. Dock kan ingen klar korrelation mellan ämnets lipofilitet (log Kow) och koncentrationen i utgående vatten ifrån reningsverk påvisas ifrån denna studie. Andra faktorer såsom kelateffekter, elektrostatisk interaktion (t ex jonbyte), kemisorption bör också beaktas för att man bättre skall förstå och kunna förutsäga hur läkemedelssubstanser fördelar sig i olika matriser i miljön.

En riskuppskattning baserad på tillgängliga ekotoxikologiska data visar på en försumbar risk för fluoxetine, paroxetine och citalopram. Dessutom ger "read-across" baserad riskkvot för oxazepam en försumbar risk även för detta ämne. Riskkvoten är dock beräknad på ekotoxikologiska data för diazepam.

För de andra ämnena som återfanns i utgående vatten: paroxetine, zolpidem, risperidone and propofol fanns inga ekotoxikologiska data att tillgå.

Tabell A Koncentrationsintervall i vatten (antal prover som analyserats inom parantes)

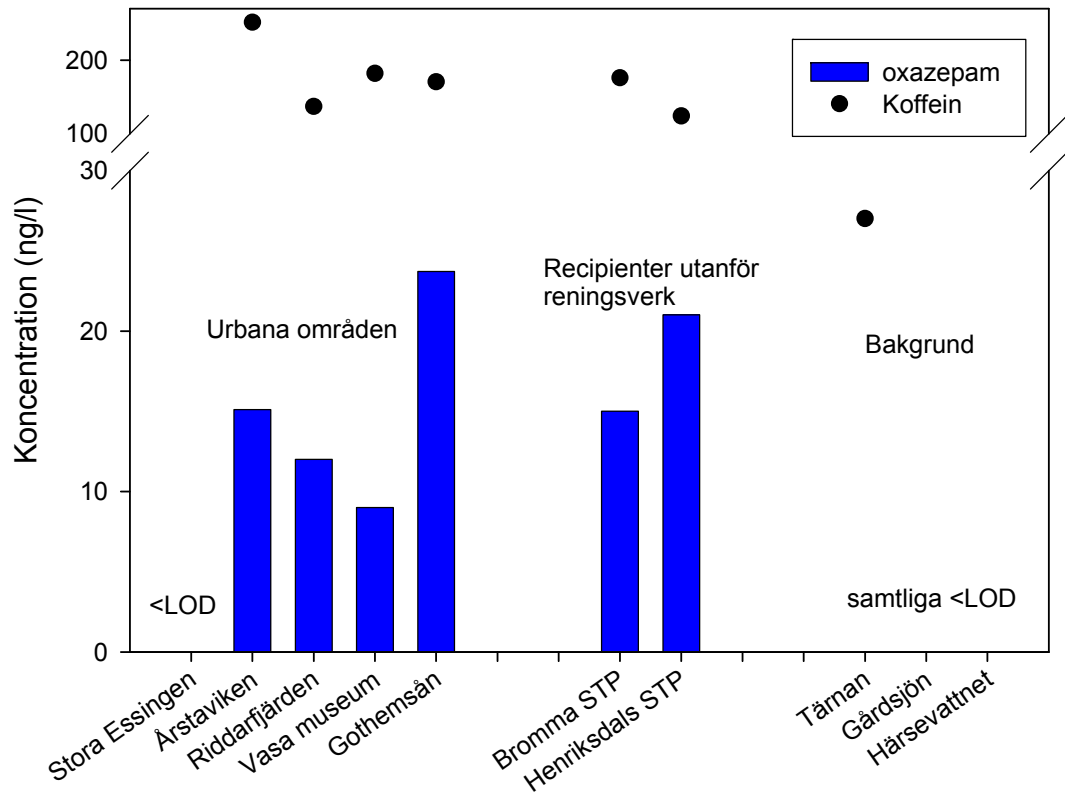
	ARV inkommande vatten (20) ng/l	ARV utgående vatten (34) ng/l	Ytvatten och dricksvatten (13), ng/l	Lakvatten (4), ng/l
<b>Fentanyl</b>	<2	<2	<2	<2
Norfentanyl*	<5	<5	<5	<5
<b>Dextropropoxyphen</b>	<2	<2	<2	<2
Norpropoxyphen*	<5	<5	<5	<5
<b>Propofol</b>	<0.6 - 29	<0.6 - 510	<0.6	<0.6 - 18
<b>Bromokriptin</b>	<2	<2	<2	<2
<b>Thioridazin</b>	<2	<2	<2	<2
<b>Clozapin</b>	<3	<3	<3	<3
<b>Risperidon</b>	<1 - 20	<1 - 8	<1	<1 - 260
<b>Zolpidem</b>	<1 - 31	<1 - 14	<1	<1
<b>Sertralin</b>	<1	<1	<1	<1
<b>Fluoxetin</b>	<1 - 66	<1 - 53	<1	<1
<b>Flunitrazepam</b>	<1	<1	<1	<1
7-Aminoflunitrazepam*	<5 - 78	<5	<5	<5 - 1 000
N-Demetyflunitrazepam*	<5	<5	<5	<5
<b>Diazepam</b>	<0.8	<0.8	<0.8	<0.8
Nordiazepam*	<3 - 28	<3 - 30	<3	<3
<b>Oxazepam<sup>a</sup></b>	33 - 1 200	79 - 1 200	<4 - 24	10 - 110
<b>Zoplikon</b>	<1	<1	<1	<1
Zoplikon-N-oxide*	<5 - 230	<5 - 89	<5	<5
<b>Citalopram</b>	12 - 180	<0.3 - 120	<0.3	<0.3 - 26
<b>Paroxetin</b>	<1 - 70	<1 - 56	<1	<1 - 1 200
<b>Caffein</b>	13 000 - 150 000	<8 - 43 000	<8 - 250	<8 - 550 000

\*metabolit till substansen ovan, <sup>a</sup>är även en metabolit till diazepam.

Tabell B Koncentrationsintervall slam, sediment, fisk (antal analyserade prover inom parantes)

	Slam (32), ng/g TS	Sediment (9), ng/g TS	Fisk (9), ng/g VV
<b>Fentanyl</b>	<1	<1	<1
Norfentanyl*	<1	<2 - 110	<2
<b>Dextropropoxyphen</b>	<0.9-1	<0.9	<0.9
Norpropoxyphen*	<1	<1	<1
<b>Propofol</b>	<0.1 - 4.5	<0.1 - 4.4	<0.1
<b>Bromocriptin</b>	<1	<1	<1
<b>Thioridazin</b>	<1	<1	<1
<b>Clozapin</b>	<0.8 - 68	<0.8	<0.8
<b>Risperidon</b>	<0.5	<0.5	<0.5
<b>Zolpidem</b>	<0.2 - 3.8	<0.2	<0.2
<b>Sertralin</b>	1.6 - 310	0.3 - 1.6	<0.3
<b>Fluoxetin</b>	<0.5	<0.5	<0.5
<b>Flunitrazepam</b>	<0.5	<0.5 - 3.3	<0.5
7-Aminoflunitrazepam*	<1	<1	<1
N-Demetyflunitrazepam*	<1	<1	<1
<b>Diazepam</b>	<0.5	<0.5	<0.5
Nordiazepam*	<1	<1	<1
<b>Oxazepam<sup>a</sup></b>	<1 - 110	<1	<1
<b>Zoplikone</b>	<1	<1	<1
Zoplikone-N-oxide*	<1	<1	<1
<b>Citalopram</b>	23 - 210	<0.5 - 1.8	≤0.3 - < 0.5
<b>Paroxetin</b>	<0.5	<1	<1
<b>Caffein</b>	<2 - 560	<2	<2

\*metabolit till substansen ovanför, <sup>a</sup>är även en metabolit till diazepam.



Figur A Uppmätt koncentrationen av oxazepam repektive koffein i ytvattenprover.



Tabell C Sammanfattning av erhållna koncentrationer i vattenprover (ng/l) från regionala reningsverk uppdelat per län.

Län	Matrix	Antal prover	Fluoxetin	Propofol	Risperidon	Zolpidem	Oxazepam	Paroxetin	Citalopram	Zopiclon N-oxid	7-Aminoflu_nitrazepam	Nordiazepam
Blekinge	Inkommande + inkommande från sjukhus	8	<1 - 66	<0.6 - 98	<1	<1 - 31	79 - 1100	<1 - 45	49 - 180	<5 - 230	<5 - 78	<3
Södermanland	Inkommande	6	<1 - 63	<0.6	<1 - 17	<1	360 - 920	<1 - 24	38 - 120	<5	<5	<3
Värmland	Inkommande	2	<1 - 66	<0.6 - 8.3	<1	<1 - 19	760 - 810	<1 - 68	51 - 106	<5	<5	<3 - 25
Blekinge	Utgående	6	<1 - 53	<0.6 - 200	<1 - 3	<1 - 31	110 - 1200	<1 - 37	51 - 125	<5	<5 - 26	<3 - 15
Dalarna	Utgående	6	<1 - 41	<0.6 - 18	<1 - 7.8	<1 - 10	470 - 850	<1 - 20	67 - 110	<5 - 89	<5	<3 - 29
Gotland	Utgående	1	<1	10	<1	14	580	56	57	<5	<5	14
Norrbottnen	Utgående	3	<1 - 30	<0.6 - 14	<1	<1 - 12	270 - 480	<1 - 26	39 - 97	<5	<5	<3 - 17
Södermanland	Utgående	8	<1 - 29	<0.6 - 1.7	<1		330 - 750	<1 - 34	<0.3 - 89	<5	<5	<3 - 26
Värmland	Utgående	2	<1	<0.6 - 14	<1	<1 - 5	800 - 980	<1	110	<5	<5	<3 - 30

Sammanfattning av koncentrationer i slamprover (ng/g TS) från regionala reningsverk uppdelat per län.

Län	Antal prover	Propofol	Clozapin	Zolpidem	Sertralin	Oxazepam	Citalopram
Blekinge	6	<0.1 - 0.4	<0.8 - 17	<0.2 - 2.2	11 - 200	<0.5 - 110	45 - 150
Dalarna	2	<0.1	<0.8 - 68	<0.2	<0.3 - 79	<0.5 - 40	74 - 210
Norrbottnen	1	<1	52	1.4	81	<1	95
Södermanland	6	<0.1 - 0.2	<0.8 - 54	<0.2 - 3.2	8 - 98	<0.5 - 45	48 - 150
Värmland	4	<0.1 - 0.3	<0.8 - 50	<0.2 - 1.7	46 - 210	<0.5 - 71	66 - 140
Västerbotten	2	<0.1	15 - 38	<0.2 - 2	140 - 300	<0.5 - 17	70 - 120



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Appendix 1-6

## 1 Introduction

As an assignment from the Swedish Environmental Protection Agency, IVL has during 2006/2007 performed a "Screening Study" of phthalates, 1,5,9-cyclododecatriene, zinc pyrithione, pharmaceuticals and chromium (VI). These substances are emitted and distributed in the environment via a variety of sources, e.g. point sources and via use in consumer products. Pharmaceuticals in particular are frequently spread by domestic use.

The overall objectives of the screening were to determine the concentrations of the selected substances in a variety of media in the Swedish environment, to highlight important transport pathways, and to assess the possibility of current emissions in Sweden. A further aim was to investigate the likelihood of atmospheric transport (phthalates, 1,5,9-cyclododecatriene and chromium) and uptake in biota.

The results are reported in five sub-reports according to Table 1.

Table 1. Substances / substance groups included in the screening

Substance / Substance group	Sub-report #.
Phthalates:	1
Di-isononyl phthalate (DINP)	
Di-isodecyl phthalate (DIDP)	
1,5,9-Cyclododecatriene (CDDT)	2
Zinc pyrithione	3
Pharmaceuticals:	4
Fentanyl, Propofol, Dextropropoxyphene, Bromocriptine, Thioridazine, Clozapine, Risperidone, Zolpidem, Sertraline, Fluoxetine, Flunitrazepam, Diazepam, Oxazepam	
Hexavalent chromium (Cr(VI))	5

This sub-report considers the screening of pharmaceuticals.

Pharmaceuticals are widely used substances. On the Swedish market there are approximately 1200 active compounds in about 7600 different products (Läkemedelsverket, 2004). During the last decade pharmaceuticals have become identified as emerging environmental contaminants (Halling-Sørensen et al., 1998, Kümmerer (ed), 2004).

The inherent bioactivity of pharmaceuticals has thus far manifested itself in the environment in a number of cases such as the adverse effects on reproduction and hormonal disturbances of aquatic organisms due to the presence of a synthetic hormone, ethinylestradiol (MacLatchey et al., 1997, Routledge et al. 1998, Larsson et al., 1999). In South East Asia, the use of the anti-inflammatory drug diclofenac in veterinary medicine has resulted in an almost complete extinction of some species of vultures, feeding on cattle carcasses. These birds have shown to experience acute kidney failure syndrome upon exposure to the drug (Oaks et al., 2004). Concerns have also been raised on the topic of bacterial resistance to antibiotics in sludge from wastewater treatment plants (Alexy et al., 2004).

Pharmaceutically active substances are developed and used because of their biological activity. Normally pharmaceuticals are classified according to their therapeutic purpose and within the subgroups of the active ingredient, by chemical structure.

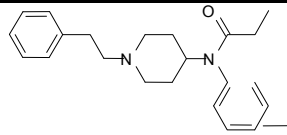
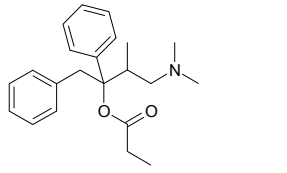
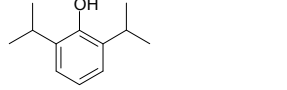
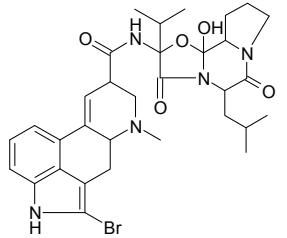
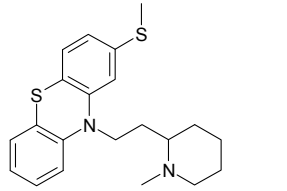
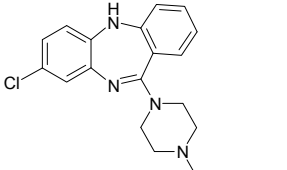
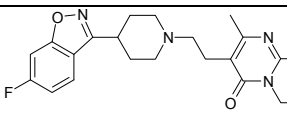
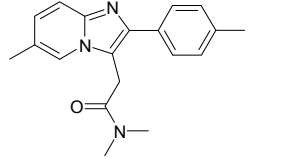
## 2 Pharmaceuticals and pharmaceutical metabolites in the screening

All pharmaceuticals included in this screening study purposely affect the human nervous system, having the Anatomical Therapeutic Chemical Classification (ATC) main code 'N'. In 2006 the Swedish consumption of drugs of this therapeutic use was 825 million Defined Daily Doses (DDDs), as defined by WHO) corresponding to a net cost of 6 140 million SEK (Apoteksbolaget, 2006). The central nervous system (CNS) represents the largest part of the nervous system, including the brain and the spinal cord. Together with the peripheral nervous system, it has a fundamental role in the control of behaviour. The CNS is contained within the dorsal cavity, with the brain within the cranial sub cavity, and the spinal cord in the spinal cavity. The basic pattern of the CNS is highly conserved throughout the different species of vertebrates and during evolution. This conservation of receptors implies that drugs with a high potency when administered to humans may have toxic effects to aquatic organisms.

The major subgroups of pharmaceuticals included in this screening study were; analgetics (fentanyl, dextropropoxyphene), anesthetics (propofol), dopaminergic agonists (bromocriptine), neuroleptics (thioridazine), anti-psychotics (clozapine and risperidone), sedatives (zolpidem), benzodiazepines (flunitrazepam, diazepam and oxazepam), and selective serotonin re-uptake inhibitors, SSRIs (sertraline and fluoxetine). The selected substances are presented in Table 2. In addition to these substances, also the most common metabolites have been included and their appearance and context is presented in Table 3.

Paliperidone, the dominant metabolite of Risperidone was purposely omitted from this study since no commercial source to pure reference standards of this compound could be identified. Instead three other high sales drugs of the main therapeutic group, 'N', were included; the sedative Zopiclone and the SSRIs Citalopram and Paroxetine. Zopiclone-N-oxide, a metabolite of Zopiclone was also included.

Table 2. Pharmaceuticals selected for the screening

Therapeutic use	Substance	Molecular structure	CAS #
Analgetics	Fentanyl		437-38-7
	Dextropropoxyphene		469-62-5
Anaesthetics	Propofol		2078-54-8
Dopaminergic agonists	Bromocriptine		25614-03-3
Neuroleptics	Thioridazine		50-52-2
Atypical anti-psychotics	Clozapine		5786-21-0
	Risperidone		106266-06-2
Non-benzodiazepine hypnotic, sedatives	Zolpidem		82626-48-0

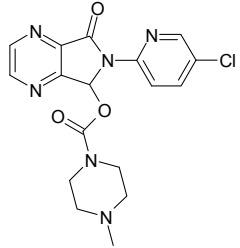
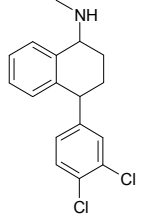
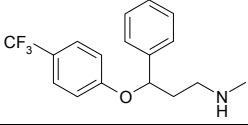
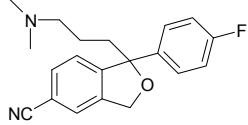
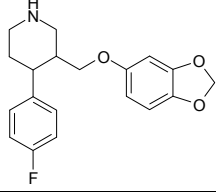
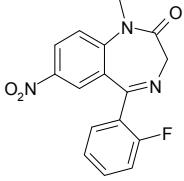
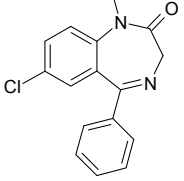
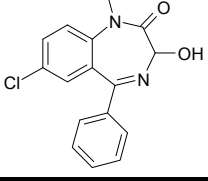
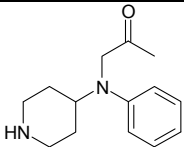
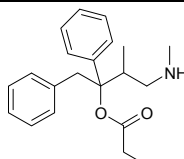
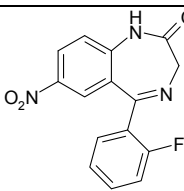
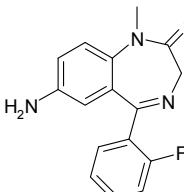
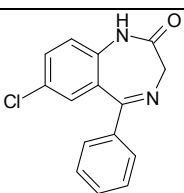
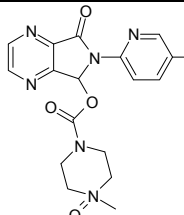
Therapeutic use	Substance	Molecular structure	CAS #
	Zopiclone		43200-80-2
SSRIs	Sertraline		79617-96-2
	Fluoxetine		54910-89-3
	Citalopram		59729-33-8
	Paroxetine		61869-08-7
Benzodiazepines	Flunitrazepam		1622-62-4
	Diazepam		439-14-5
	Oxazepam		604-75-1



Table 3. Metabolites included in the screening

Metabolite of	Substance	Molecular structure	CAS #
Fentanyl	Norfentanyl		1609-66-1
Dextropropoxyphene	Norpropoxyphene		3376-94-1
Flunitrazepam	N-demethylflunitrazepam		2648-00-2
Flunitrazepam	7-aminoflunitrazepam		34084-50-9
Diazepam	Nordiazepam		1088-11-5
Zopiclone	Zopiclone N-oxide		43200-96-0

### 3 Therapeutical use

Pharmaceuticals are administered orally, dermally or intravenously depending on the substance and the medical circumstances (Kümmerer, 2004). According to the legislation pharmaceuticals are classified as “substances that are intended to be supplied to humans or animals in order to prevent, point out, relieve or cure a disease or a symptom of a disease” (Läkemedelsverket, 2004; own translation). The purpose of the chemical is a central part of the definition. Below the therapeutical use and consumption of the drugs included in this screening are described and a summed sales volume chart displays how much of each pharmaceuticals is being sold (Figure 1).

The use of pharmaceuticals is regulated within the European Union. Regulations are concerned with both the importance for and the possible impact of the substance on human health. It is also an area that takes national economic and social interests into consideration. The regulation is based on Directive 2001/83/EC of the European Parliament as well as on the Council of 6 November 2001 on the Community code related to medicinal products for human use. Further, it is amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

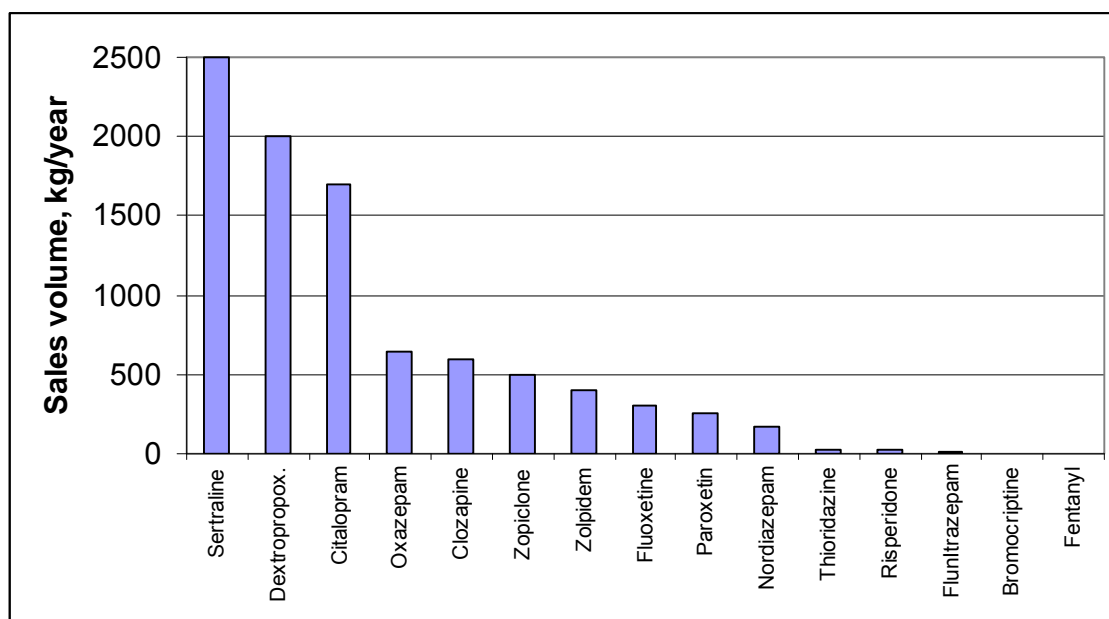


Figure 1 . Estimated sales volumes in kg/year (2006). Due to the administrative route for propofol no estimation of sold amounts in kg could be made for this substance. Regarding Fentanyl two formulations (injection based) do not have a DDD from WHO, thus the overall sales could be significantly higher.

## 3.1 Analgetics

Analgetics is the collective name for pharmaceuticals with the therapeutic function to release pain.

### 3.1.1 Fentanyl

Fentanyl (ATC N02AB03) is an opioid, i.e., it has got an activity towards the opioid receptor in the brain. Opioids are synthetic versions of the naturally occurring opiates. Fentanyl is a heroine derivative and with heroine as a blue print structure, the molecule has been rendered a higher lipophilicity which enables the drug to easier pass the blood-brain barrier (van Bever et al., 1974). Fentanyl has become a drug of abuse since its potency is several orders of magnitude higher than that of heroine. In Russia it has also been used as a component in combat gas (*incapacitating gas*). In Sweden fentanyl is only available by prescription from a physician and all fentanyl sold as fentanyl is formulated as depot patches and plasters for controlled release. Fentanyl citrate is sold as tablets and as infusion fluid. Fentanyl is being excreted mainly in the urine, primarily as different metabolites. Less than 10 % of administered dose is excreted unchanged. The most important metabolite is norfentanyl.

The number of defined daily doses (DDDs) sold in Sweden in 2006 reached at least 3 022 003 DDDs which corresponds to 2 - 4 kg. It is not straightforward to encompass also the amount of the drug sold in the depot formulation.

### 3.1.2 Dextropropoxyphene

Dextropropoxyphene (ATC N02AC04), like codeine, is a "weak" opioid. Codeine is more commonly used, however some individuals (approximately 10-20% of the Caucasian population) are unable to metabolize Codeine, due to poor functioning of the enzyme CYP2D6. It is for that fraction of the population that dextropropoxyphene is particularly useful, as its metabolism does not require CYP2D6. Chemically, dextropropoxyphene is an optical isomer of levopropoxyphene. The racemic mixture is called propoxyphene. Preparations on the Swedish market that contain dextropropoxyphene include distalgescic and doloxene (fass.se). In Sweden dextropropoxyphene is sold in a galenic formulation as a salt of naphthyl sulfonic acid. Dextropropoxyphene is metabolised in the liver and by N-demethylation of the mother compound (phase I-metabolism) the main metabolite, norpropoxyphene, is formed. This metabolite is excreted in the urine.

In 2006 8 345 825 DDDs of dextropropoxyphene were sold as well as 1 500 DDDs where dextropropoxyphene is included in combination with other drugs (ATC N02AC54). This corresponds to 2 000 kg of the substance.

## 3.2 Anaesthetics

Anaesthetics are the collective name for pharmaceuticals with the therapeutic function to release pain, sedate and induce narcosis. Anaesthesia has traditionally meant the condition of having the perception of pain and other sensations blocked. This allows patients to undergo surgery and other procedures without the distress and pain they would otherwise experience. Local anaesthetics release pain.

### 3.2.1 Propofol

Propofol (ATC N01AX10) is a short-acting intravenous anaesthetic agent used for the induction of general anaesthesia in adult patients and paediatric patients older than 3 years of age. The drug is administered intravenously by medical care personnel and it is thus not used at home. By appearance as a pure chemical it is a water-immiscible oil (Fowler et al., 2004). Propofol is metabolised by hepatic glucuronidation, i.e. conjugation in the liver (phase II metabolism). Also some hydroquinone analogues of the drug are excreted.

Since propofol is only administered intravenously no DDD-definition is applicable, hence it is difficult to estimate the total consumption of the drug in Sweden. Swedish hospitals and health care facilities spent 55.6 million SEK on propofol in 2006.

## 3.3 Dopaminergic agonists

A dopamine agonist is a compound that activates the same receptors as the neurotransmitter dopamine. It is used for treating Parkinson's disease among other symptoms.

### 3.3.1 Bromocriptine

Bromocriptine (ATC N04BC01) is one of several dopaminergic agonists. The consumption in Sweden 2006 was 28 089 DDD (40 mg) corresponding to 1.1 kg. Bromocriptine is also used for its ability to lower prolactin levels. It is used in the treatment of amenorrhea (lack of a menstrual period), persistent breast milk production, infertility, and other conditions associated with high prolactin levels caused by prolactin-secreting tumours. In this use (ATC G02CB01) 952 147 DDD (5 mg) corresponding to 4.8 kg was sold. Thus, the total consumption of bromocriptine was 5.9 kg in 2006.

## 3.4 Neuroleptics

### 3.4.1 Thioridazine

Thioridazine (ATC N05AC02) is an antipsychotic drug previously widely used in the treatment of schizophrenia and psychosis. It was sold under the trade name Mallorol, but was drawn back from the Swedish market at the end of 2004 due to reports on serious heart arrhythmias. It can still be sold to specific patients on licences issued by Medical Products Agency (Läkemedelsverket). The sales in 2006 was 92 600 DDD corresponding to 28 kg. This can be compared to the 873 054 DDD (262 kg) sold in 2004.

## 3.5 Atypical anti-psychotics

The atypical anti-psychotics (also known as second generation anti-psychotics) are a class of prescription medications used to treat psychiatric conditions. Most atypical anti-psychotics are also approved for use in the treatment of schizophrenia. Some carry approved indications for acute mania, bipolar mania, psychotic agitation, bipolar maintenance, and other indications.

### 3.5.1 Clozapine

Clozapine (ATC N05AH02) was the first of the atypical anti-psychotics to be developed and the first to be approved medication for treatment-resistant schizophrenia and for reducing the risk of suicidal behaviour in patients with schizophrenia (Bandelow et al. 2004). Clozapine is extensively hepatically metabolized involving many CYP-450 isoenzymes and eliminated in the urine (50 %) and faeces (30 %). The main metabolite formed is the de-methylated analogue, norclozapine. It has a similar pharmacological activity as the mother compound, however with a lower potency and shorter duration (fass.se).

In 2006 1 855 751 DDDs of clozapine were sold in Sweden which corresponds to 600 kg.

### 3.5.2 Risperidone

Risperidone (ATC N05AX08) is a benz-isooxazole derivate and is most often used to treat delusional psychosis (including schizophrenia). Risperidone is also used to treat some forms of bipolar disorder, psychotic depression, obsessive-compulsive disorder and Tourette syndrome (FDA, 2006). The drug is a selective monoaminergic antagonist ("blocker") with high affinity for serotonergic 5HT<sub>2</sub>- and dopaminergic D<sub>2</sub>-receptors. Risperidone is phase I-metabolised through the CYP 2D6 enzymes to 9-hydroxyrisperidone (paliperidone). The mother compound and the main metabolite have very similar pharmacological activity.

Risperidone is now the most commonly prescribed antipsychotic medication in the United States. In 2006 4 218 079 DDDs of risperidone, which corresponds to 8-20 kg, were sold in Sweden.

## 3.6 Non-benzodiazepines (hypnotics and sedatives)

The non-benzodiazepines are new drugs whose benefits are very similar to those of the benzodiazepines (see below), but which have much fewer side effects. Thus far, the three main groups are imidazopyridines (Zolpidem), pyrazolopyrimidines and cyclopyrrones (Zopiclone).

### 3.6.1 Zolpidem

Zolpidem (ATC N05CF02) is a non-benzodiazepine of the imidazopyridine-group that potentiates gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to benzodiazepine type 1 (BZ1) receptors (Depoortere et al., 1986). Zolpidem is used for the short-term treatment of insomnia (Schlich et al., 1991). Zolpidem is eliminated through the liver (cytochrome P450III<sub>A</sub>) as pharmacologically inactive compounds in urine (56 %) and faeces (29-42 %).

In 2006, 42 606 652 DDDs of zolpidem, which corresponds to 400 kg were sold in Sweden.

### 3.6.2 Zopiclone

Zopiclone (ATC N05CF01) is a hypnotic agent non-benzodiazepine of the cyclopyrrone group that is used in the treatment of insomnia. Zopiclone, as traditionally sold worldwide, is a racemic mixture of two stereoisomers, only one of which is active. Zopiclone metabolised in the liver by phase I-decarboxylation to N-Desmethylzopiclone (15 % of the dose) and zopiclone N-oxide (11

% of the dose). Both of these metabolites have considerably lower pharmacological activity. About 5 % of the administered zopiclone dose is excreted unchanged (fass.se).

In 2006, 60 304 311 DDDs of zopiclone were sold in Sweden. This corresponds to 500 kg of the substance.

## 3.7 Benzodiazepines

Benzodiazepines psycho-active drugs are considered as minor tranquilizers with varying hypnotic, sedative, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties which are brought upon by this class of drug slowing down the central nervous system. This makes benzodiazepines useful in treatment of anxiety, insomnia, agitation, seizures, muscle spasms, and also alcohol withdrawal.

### 3.7.1 Flunitrazepam

Flunitrazepam (ATC N05CD03) (formerly marketed under the trade name Rohypnol in North America) is a powerful hypnotic drug which is a benzodiazepine derivative. It has powerful hypnotic, sedative, anxiolytic, and skeletal muscle relaxant properties (Cano et al., 1977). The potency of the drug in combination with the very frequent abuse pattern (actually the origin of criminal indictments like *Drug-facilitated sexual assault* in the US and *Drug-facilitated robbery* in the UK, BBC Online, 990320) has led to attempts in the US to ban flunitrazepam from the market (NDIC, 2006). In a first step, sales of pharmaceutical formulations with the higher doses (2-5 mg) have now been stopped permanently. Also in Sweden flunitrazepam is strongly associated with violence and criminal activities (Expressen, 2004), flunitrazepam is primarily metabolised as N-demethyl-flunitrazepam (with similar pharmacological activity) and 7-aminoflunitrazepam. Excretion is mainly facilitated as glucuronides of the metabolites in urine. About 10 % of the flunitrazepam dose is excreted in faeces (fass.se).

In 2006 10 412 505 DDDs of flunitrazepam were sold in Sweden. This corresponds to 10 kg of the substance.

### 3.7.2 Diazepam

Diazepam (ATC N05BA01) is marketed under brand names like Valium® (US) and Stesolid (Sweden). The pharmaceutical is a core medicine in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system. Diazepam is used to treat a wide range of conditions and is one of the most frequently prescribed benzodiazepines. This led to diazepam to become the top-selling pharmaceutical in the United States from 1969 to 1982. While psychiatrists continue to prescribe diazepam for the short-term relief of anxiety, neurology has taken the lead in prescribing diazepam for the palliative treatment of certain types of epilepsy and spastic activity, e.g., forms of paresis (Sieghart W, 1994). Diazepam is also found in nature. Several plants, such as potato and wheat, contain trace amounts of naturally occurring diazepam and other benzodiazepines. The main active metabolite of diazepam is desmethyldiazepam (also known as nordazepam or nordiazepam). Diazepam's other active metabolites include temazepam and oxazepam (Baselt RC, 2002, Chamberlain J, 1995, Wong S, 1997). These metabolites are conjugated with glucuronides, and are subsequently being excreted primarily in the urine (Figure 2).

In 2006 17 317 862 DDDs of diazepam, corresponding to 170 kg, were sold in Sweden.

### 3.7.3 Oxazepam

Oxazepam (ATC N05BA04) (marketed under brand names Sobril®) is a metabolic by-product of diazepam. It is an intermediate acting benzodiazepine with a slow onset of action, so it is usually prescribed to individuals who have trouble staying asleep, rather than falling asleep (Sonne et al., 1988). The metabolic pattern of oxazepam is depicted in Figure 2 (Baselt RC, 2002, Chamberlain J, 1995).

In 2006 12 779 117 DDDs of oxazepam, corresponding to 640 kg, were sold in Sweden.

## 3.8 SSRI s

Selective serotonin re-uptake inhibitors (SSRIs) are a class of antidepressants used in the treatment of depression, anxiety disorders and some personality disorders. SSRIs increase the extra cellular level of the neurotransmitter serotonin by inhibiting its reuptake into the pre-synaptic cell, increasing the level of serotonin available to bind to the postsynaptic receptor.

### 3.8.1 Sertraline

Sertraline hydrochloride (ATC N06AB06) (also labelled under numerous brand names like Zoloft) is specifically used in therapies for general anxiety disorder, binge eating disorder, and premature ejaculation. One of the main advantages of sertraline is the high specificity; sertraline does not affect the psycho-motoric and cognitive functions of the patients (Kronig et al., 1999). Sertraline is primarily phase I-metabolised in the liver to the pharmacologically inactive N-desmethylsertraline (CAS # 87857-41-8). In 2006 49 129 673 DDDs of sertraline, corresponding to 2 500 kg, were sold in Sweden.

### 3.8.2 Fluoxetine

Fluoxetine hydrochloride (ATC N06AB0, sold under names such as Prozac in the US and Fontex in Sweden) is an antidepressant drug used medically in the treatment of depression, body dysmorphic disorder, obsessive-compulsive disorder, bulimia nervosa, premenstrual dysphoric disorder, hypochondrias and panic disorder (Walsh et al., 2006). The liver metabolises fluoxetine into norfluoxetine, a desmethyl metabolite from phase I-metabolism, which is also a serotonin reuptake inhibitor. Fluoxetine has a remarkably long half-life in the body 4-6 days, and also the metabolite is very stable having a half-life of 4-16 days (fass.se). This may be indicative of extended persistence in the environment too.

In 2006 14 789 338 DDDs of fluoxetine, corresponding to 300 kg, were sold in Sweden.

### 3.8.3 Citalopram

Citalopram (ATC N06AB04) (sold under trade names like Cipramil in Sweden) is an antidepressant drug used to treat depression associated with mood disorders. It is also used on occasion in the treatment of body dysmorphic disorder and anxiety (Sindrup et al., 1992). The drug citalopram is a

racemic mixture but now also the pure S-enantiomer of the racemic citalopram, escitalopram, is sold as a pharmaceutical (CipraleX® in Sweden, Denmark and the US). Citalopram is phase I-metabolised to desmethylcitalopram, di-desmethylcitalopram and citalopram-N-oxide. The first two of these metabolites have also pharmacological SSRI-activity, but they have lower potency and selectivity (fass.se).

In 2006, 76 311 712 DDDs of citalopram, corresponding to 1 530 kg were sold in Sweden. The contribution from the enantio-pure escitalopram (ATC N06AB10) was 13 307 333 DDDs during that year (corresponding 130 kg), giving an estimated total consumption of 1 700 kg.

### 3.8.4 Paroxetine

Paroxetine (ATC N06AB05) or paroxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) antidepressant. It was released world wide in 1992 and has since become one of the most prescribed antidepressants on the market due to its apparent efficacy in treating depression as well as a spectrum of anxiety disorders ranging from panic attacks to phobias (Baldwin et al., 1999). Paroxetine is the most potent selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant effects. Paroxetine is metabolised to a plethora of different polar and pharmacologically inactive metabolites. About 2 % of the administered dose of paroxetine is excreted unchanged in the urine and < 0.5 % is excreted unchanged in the faeces.

In 2006 12 783 697 DDDs of paroxetine, corresponding to 260 kg, were sold in Sweden.

## 4 Environmental effects and fate

Pharmaceutical agents may enter the environment mainly via two pathways, the industrial route or the domestic route. The pharmaceuticals will be administered to a patient, either at home or in hospitals and the substances are mainly reaching the community sewage treatment plants (STPs) via excretion (Kümmerer, 2004). In the STPs they will be degraded totally, partially or be released intact to recipient water systems. The pharmaceuticals may also be deposited as waste. Point discharges from the pharmaceutical production plants have been assumed to be limited since pharmaceuticals are high cost chemicals and the handling of the chemicals often is performed in closed facilities. However, recent findings from environmental monitoring in India where extremely high concentrations of ciprofloxacin were detected in effluent waters from several production sites has put this issue on the agenda (Larsson et al., 2007).

### 4.1 Ecotoxicity

In the report from the Swedish Medical Product Agency on environmental effects of pharmaceuticals (Läkemedelsverket, 2004), 30 pharmaceutically active compounds were classified with regard to aquatic toxicity, according to the regulation of the Swedish Chemicals Agency for the classification and labelling for chemical products. That classification of the pharmaceuticals performed by the Swedish Medical Product Agency, with respect to the substances included in this study, is rather incomplete. However, relevant information on eco-toxicity data extracted from that report is presented in Table 4.



Table 4. Toxicity and environmental data (Läkemedelsverket, 2005)

Substance	Toxic values	PNEC (µg/L)	Bioaccumulation	Persistence
Fentanyl	<b>H</b>		Potential for bioacc.	« persistent »
Dextropropoxyphene	5 invertebrates tested, <i>Brachionus calyciflorus</i> most sensitive. EC <sub>50</sub> (24 h) 5.4 mg/l	5.4	No data	No data
Propofol	<b>VT</b>		No data	No data
Bromocriptine	<b>VT</b>		Potential for bioacc.	« persistent »
Thioridazine	<b>VT</b>		No data	« persistent »
Clozapine	<b>VT</b>		No data	« persistent »
Risperidone	<b>T</b>		Potential for bioacc.	« persistent »
Zolpidem	<b>T</b>		Potential for bioacc.	« persistent »
Sertraline	<b>VT</b>		No potential for bioacc.	No data
Fluoxetine	Extensive data, <i>Oryzias latipes</i> (fish) most sensitive. LOEC (reprod.) 0.1 µg/l		No potential for bioacc.	« persistent »
Flunitrazepam	<b>H</b>		No potential for bioacc.	« persistent »
Diazepam	5 invertebrates tested, <i>Daphnia magna</i> most sensitive. EC <sub>50</sub> (24 h) 14.1 mg/l	14.1	No data	No data
Oxazepam	No data		No data	No data
Zopiclone	<b>T</b>		No data	« persistent »
Zopiclone N-oxide	No data		No data	No data
Citalopram	No data		No data	No data
Paroxetine	<b>T</b>		No potential for bioacc.	« persistent »
Norfentanyl	No data		No data	No data
Norpropoxyphene	No data		No data	No data
Norclozapine	No data		No data	No data
Norfluoxetine	No data		No data	No data
N-demethyl-flunitrazepam	No data		No data	No data
7-amino-flunitrazepam	No data		No data	No data
Nordiazepam	No data		No data	No data

'VT' = Very toxic, EC<sub>50</sub> < 1 mg/l, 'T' = Toxic, 10 mg/l > EC<sub>50</sub> > 1 mg/l, 'H' = Harmful, 100 mg/l > EC<sub>50</sub> > 10 mg/l.

In a Swedish initiative started by the Swedish Association of the Pharmaceutical Industry in 2005, pharmaceutical companies have voluntarily been submitting basic data sets for an environmental risk- and hazard classification, publicly available at the web site [www.fass.se](http://www.fass.se). This is another potentially good source for environmentally relevant data. However, not all pharmaceuticals sold in Sweden have yet been classified. In Table 5 eco-toxicological data as well as other hazard parameters are listed for the compounds relevant to this study classified at [fass.se](http://fass.se) thus far.

Table 5 Hazard and risk assessment of pharmaceuticals (fass.se).

Substance	Toxic values	Bio-accumulation	Persistence	PNEC µg/l	Risk classification
Sertraline	EC <sub>50</sub> (14 days), <i>Pseudokirchneriella subcapitata</i> (Green algae), 56 µg/l	No potential for bioacc., log Kow < 3	"...slowly degraded in the environment."	0.056	PEC/PNEC = 6.4 → " .. the medicine has been considered to result in <b>moderate</b> environ. risk"
Fluoxetine	EC <sub>50</sub> (FDA TAD 4.01). <i>Pseudokirchneriella subcapitata</i> (Green algae) 27.3 µg/l	No potential for bioacc., log Kow < 3	"...slowly degraded in the environment." (OECD 301B, FDA TAD 3.11)	0.11	PEC/PNEC = 0.14-0.4 → " .. the medicine has been considered to result in <b>low</b> environ. risk"
Citalopram	EC <sub>50</sub> (48 h), <i>Acartia tonsa</i> (Zooplankton) 4.9 mg/l	Potential for bioacc. Log Kow > 3	"...slowly degraded in the environment."	4.9	PEC/PNEC = 0.049 → " .. the medicine has been considered to result in <b>insignificant</b> environ. risk"
Paroxetine	LC <sub>50</sub> (96 h), <i>Lepomis macrochirus</i> (fish) 1.6 mg/l	No potential for bioacc., log Kow < 3	"...slowly degraded in the environment." (FDA TAD 3.11)	1.6	PEC/PNEC = 0.025 → " .. the medicine has been considered to result in <b>insignificant</b> environ. risk"

PEC (predicted environmental concentration) is based on current sales data, combined with data on human metabolism and removal rate in the STP. PNEC (predicted no effect concentration) is based on the toxicity towards the most sensitive aquatic species tested (3 species req.) combined with an assessment factor.

## 4.2 Physico-chemical properties

Pharmaceutical chemicals are often complex molecules with physico-chemical properties depending on pH (e.g. dependence of log K<sub>ow</sub>). Under environmental conditions they can be neutral, cationic, anionic or zwitter ionic and often have basic or acidic functionalities.

In order to highlight the likely fate and partitioning behaviour of the pharmaceuticals it is of importance to estimate important partitioning parameters such as water solubility and log K<sub>ow</sub>.

Table 6. Physico-chemical properties of selected pharmaceuticals and their metabolites

Substance	Mw	W <sub>sol</sub> (mg/l) <sup>a</sup>	V <sub>p</sub> mm Hg (calc.) <sup>b</sup>	pK <sub>a</sub> <sup>a</sup>	Log K <sub>ow</sub> <sup>a</sup>	BCF (calc.) <sup>c</sup>
Fentanyl	336.48	200 (exp)	5.29E-09	9.45 (calc.) base	4.05 (exp)	260
Norfentanyl	232.32	-	-	10.1 (calc.) base	2.01 (calc.)	9
Dextropropoxy- phene	339.48	3.32 (exp)	5.54E-07	9.35 (calc.) base	4.18 (exp)	330
Norpropoxyphene	325.45	-	-	10.4 (calc.) base	4.28 (calc.)	1600
Propofol	178.27	124 (calc.)	3.05E-03	11.1 (exp) acid	3.79 (exp)	170
Bromocriptine	654.6	N/A	-	N/A	4.69 (calc.)	N/A
Thioridazine	370.58	0.034 (calc.)	1.42E-09	9.5 (exp) base	5.9 (exp)	7000
Clozapine	326.83	11.8 (calc.)	9.48E-09	7.5 (exp) base	3.23 (exp)	61
Norclozapine	312.80	-	-	9.2 (calc.) base	1.93 (calc.)	21
Risperidone	410.49	-	-	9.4 (calc.) base	3.49 (calc.)	97
Zolpidem	307.39	-	-	6.2 (exp) base	3.85 (calc.)	180
Sertraline	306.23	-	-	9.8 (calc.) base	5.29 (calc.)	2300
Fluoxetine	309.33	60.3 (calc.) <i>6.84 at pH 7 acc. to manufact.</i>	2.52E-05	10.3 (calc.) base	4.05 (exp)	260
Norfluoxetine	295.30	-	-	10.1 (calc.) base	3.79 (calc.)	330
Flunitrazepam	313.29	72.8 (calc.)	2.54E-09	1.7 (calc.) base	2.06 (exp)	7.7
N-demethyl flunitrazepam	254.26	234 (calc.)	2.84E-08 (calc.)	2.8 (calc.) base	2.32 (exp)	12
7-amino flunitrazepam	283.31	1190 (calc.)	6.37E-09	3.2 (calc.) base	1.3 (exp)	2
Diazepam	284.75	50 (exp)	2.78E-08	3.4 (exp) base	2.82 (exp)	30
Oxazepam	286.72	179 (calc.)	3.76E-12	10.6-11.4 (calc.)	2.24 (exp)	11
Nordiazepam	270.72	57 (calc.)	6.44E-09	2.8 (calc.) acid	2.93 (exp)	4.1
Zopiclone	388.81	-	-	7.8-9.6 (calc.)	1.54 (calc.)	3
Zopiclone N-oxide	404.81	-	-	2.7, 9.5 (calc.)	0.02 (calc.)	3.2
Citalopram	324.40	-	-	9.8 (calc.) base	3.74 (calc.)	150
Paroxetine	329.37	-	-	10.2 (calc.) base	3.95 (calc.)	900

<sup>a</sup>Values retrieved from the ChemIDplus Advanced-website, either experimental or generated by QSAR.

<sup>b</sup>Values retrieved from the ChemIDplus Advanced-website, using the internal QSAR-engine.

<sup>c</sup>BCF-values generated from the PBT-profiler website, using the internal QSAR-engine.

In the mere absence of publicly available experimental data on environmentally relevant parameters such as water solubility, log K<sub>ow</sub>- and log K<sub>oc</sub>-values, an open-user QSAR-engine have been used to calculate the data above (Table 6). All pharmaceuticals and metabolites included in this study except for propofol, are rather polar amines, and hence the QSAR-calculations should be considered as indicative only. In cases where experimental data have been identified, the relative error of the QSAR-calculation has been assessed. As for the pK<sub>a</sub>-values, the QSAR-model seems to overestimate the pK<sub>a</sub> by 0.5 - 1 units. Log K<sub>ow</sub> was overestimated by 0.1 - 0.7 logarithmic units in those cases where experimentally determined values have been compared with the values of the QSAR-model. This uncertainty will be superimposed onto the BCF-data (generated by another

QSAR-engine). Furthermore, the QSAR-model used for the prediction of solubility, pKa- and log Kow- values mostly predicts a lower log Kow-value and a higher water solubility for the metabolites compared to the mother compound, 7-aminoflunitrazepam being the major exception to this observation. The fact that the metabolites seem less unpolar than the original active drug is in agreement with the scientific rationale on metabolism.

The dopaminergic agonist bromocriptine is a peptide-like macromolecule and hence the QSAR-model used above is probably prone to poorly accommodate such a molecule within the model, and the properties of the substance are thus neglected.

### 4.3 Environmental fate

Almost all compounds in Table 6 can be considered as bases, i.e., they have the propensity to accept a hydrogen ion (mostly at the sec-amine functionalities in the structure). At environmentally relevant pH-regions ( $8 > \text{pH} \geq 3$ ), these substances are protonated and have a localised positive charge in the chemical structure. Propofol is an acidic compound however, and consequently it is neutral in environmentally relevant pH-region while oxazepam, nordiazepam and zopiclone possesses several ionisable groups and may have several pKa-values within this pH-regime.

From the log Kow-values it is almost common practice to predict log Koc-values, i.e., the partitioning coefficient of the substance between the phase of organic carbon in a solid media (sludge, soil, sediment), and octanol. In this particular case such procedure is highly arguable since the calculated log Kow-values used in such prediction, are already associated with uncertainty.

However, the physico-chemical data (water solubility, log Kow and the propensity to become ionised) altogether clearly pinpoints water as the most relevant medium for environmental presence.

In an experimental study investigating the dissipation times ( $DT_{50}$ ,  $DT_{90}$ ), sediment sorption and persistence, diazepam was classified as a “high persistence chemical” whereas oxazepam was classified as a “moderate persistence chemical” (Löffler et al., 2005). Also the SSRI-drugs (citalopram, fluoxetine, paroxetine and sertraline) seem to be present in the solid phase, mainly because of their large log Koc-values,  $\log Koc > 4.3$ , as estimated from an investigation by Johnson et al. (Johnson et al, 2005).

The partitioning of released drug residues into other compartments than water, i.e., sediment, may thus cause a reservoir from which SSRIs may be re-released into surface waters and furthermore indicates the potential susceptibility of benthos. Johnson et al., also found model evidence that the average removal rate of SSRIs and other anti-depressants (41 compounds altogether) in the model STP was rather low, 5 % average removal. As a potential remedy, fluoxetine have shown to be prone to photolysis, both direct photolysis and indirect photolysis mediated by hydroxyl radicals (Lam et al., 2005)

## 5 Metabolism and fate of the metabolites

Many pharmaceuticals are bio-transformed in the body, which may lead to a change in the chemical structure of the active component and a change in pharmaceutical as well as in physico-chemical properties. This may lead to lower activity as well as enhanced water solubility. However, metabolism of a substance is in most cases not complete and excretion rates range from 0-100% (Kümmerer, 2004).

Metabolism in humans may occur through two major important pathways. Phase I metabolism occurs through modification of the active compound by hydrolysis, oxidation, reduction, alkylation and dealkylation. Phase II metabolites are phase I metabolites which have been modified by glycoside conjugation i.e. glucuronidation (conjugation with glucuronic acid) or sulphate conjugation (formation of sulphate esters; Kümmerer, 2004). During the phase II metabolic glucuronidation pathway the liver enzymes involved are aimed to render the metabolites more polar than the mother compound, thus increasing excretion rates. Chemically, glucuronidation involves the attachment of a glucuronic acid unit to any of the hetero atoms of the pharmaceutical mother compound (e.g., O- glucuronidation or N- glucuronidation). Whether glucuronidation takes place at the oxygen rather than nitrogen hetero atom has consequences for the STP-process. O-glucuronidated compounds are very often transformed in the STP environment back to the mother compound whereas N-glucuronidated drugs seem stable enough to pass the STP process without reformation of the mother compound (Möhle et al., 2001, Ternes et al., 1999, Kozak et al., 2001).

Pharmaceuticals being excreted mainly as a glucuronide- or sulphate ester conjugate, with only a minor fraction excreted as the mother compound, may thus end up in higher STP effluent concentration than the corresponding concentrations measured in the STP-influent stream.

The pharmaceuticals metabolised through a phase I metabolic pathway may still possess pharmacological and/or eco-toxicological properties as metabolites. Often, the phase I metabolites are very structurally similar compared to the mother compound. Several phase I-metabolites of included drugs only differs from the mother compound in the methylation of a sec-amine group, reduction of a nitro group or the hydroxylation of carboxylic oxygen. If relevant data on eco-toxicology, persistence and bioaccumulation of the mother compound are scarce in the scientific literature, the situation is even less encouraging when it comes to the metabolites.

The metabolic pathway of diazepam (in fact valid for all 1,4-benzodiazepines) is a special case, in which one of the phase I metabolites excreted is another potent drug; oxazepam, and where a substantial fraction of the both the mother compound and the main phase I-metabolites end up as a glucuronidated conjugate in the urine (Figure 2). The concentration of oxazepam in STP-samples may thus be the result of the consumption of a mere list of benzodiazepines; diazepam, medazepam (CAS # 2898-12-6), temazepam (CAS # 846-50-4), demoxazepam (CAS # 963-39-3), prazepam (CAS # 2955-38-6), chlordizepoxid (CAS # 438-41-5). The STP influent concentration of oxazepam may thus be a summed metabolic product of several other drugs, as well as reflecting the actual consumption of oxazepam itself. In the STP effluent, also the contribution of re-formed oxazepam (from digested oxazepam glucuronide) should be included.

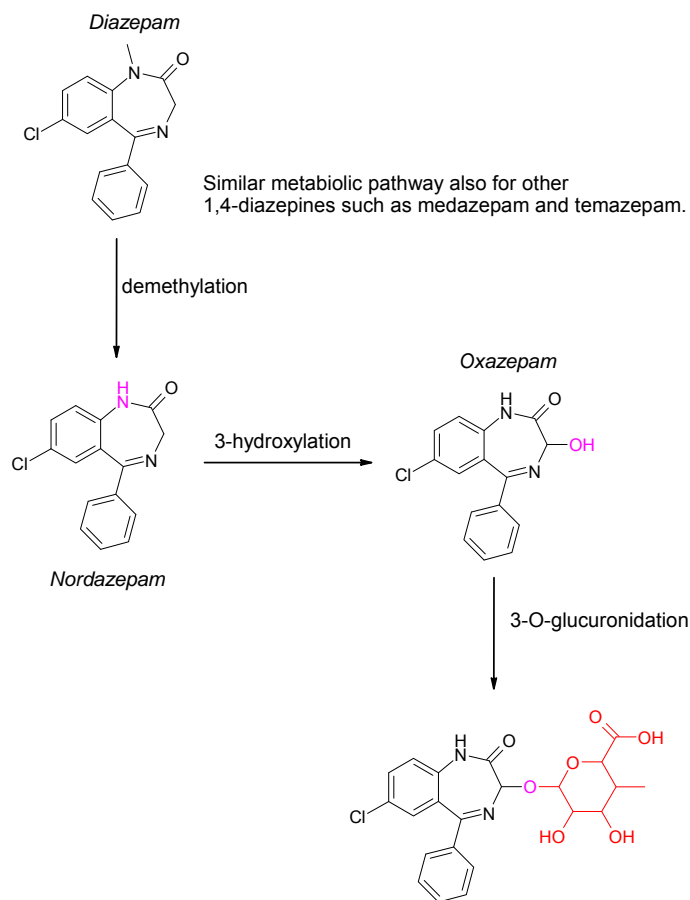


Figure 2 . The metabolic pathway of diazepam

When authorities and other stakeholders perform theoretical risk assessment on the environmental impact of a pharmaceutical, a way to reduce the predicted environmental concentrations (PECs) is to take human metabolism into consideration (in what form the pharmaceutical is excreted from the body). If the pharmaceutical leaves the body preferentially in any other form than the originally ingested, the risk assessment should preferably be performed for this compound instead of the mother substance. However, the stability of the metabolites can dramatically alter the results of such reduction if, as in the case of diazepam, re-transformation back to the mother compound during the STP process occurs. Thus, the substance can despite being excreted in another form; reach the environment as the mother compound.

## 6 Previous investigations in the environment

Data of environmental concentrations of the pharmaceuticals included in this screening found in the literature is given in Table 7. There is a general lack of data of measured environmental concentrations (MEC) for some of the included pharmaceuticals which may be related to issues such as analytical challenges, cost and availability of references standards.

Table 7. Previous investigations in the environment

Substance	Matrix	Concentration	Reference
Risperidone	STP Effluent water	< 0.0005 µg/l	Vanderford et al., 2006
Dextropropoxyphene	Surface water	~ 1 µg/l	Richardson et al., 1985
Sertraline	STP Influent water	0.0018 – 0.0025 µg/l	Vasskog et al., 2006
Sertraline	STP Effluent water	0.0009 – 0.002 µg/l	Vasskog et al., 2006
Fluoxetine	STP Influent water	0.0004 – 0.0024 µg/l	Vasskog et al., 2006
Fluoxetine	STP Influent water	0.017 µg/l	Vanderford et al., 2006
Fluoxetine	STP Effluent water	0.038 – 0.099 µg/l	Metcalfe et al., 2003
Fluoxetine	STP Effluent water	0.54 µg/l	Weston et al., 2001
Fluoxetine	STP Effluent water	0.0013 µg/l	Vasskog et al., 2006
Fluoxetine	STP Effluent water	0.025 µg/l	Vanderford et al., 2006
Fluoxetine	STP recipient water	0.013 – 0.046 µg/l	Metcalfe et al., 2003
Fluoxetine	Surface water	0.012 µg/l	Kolpin et al., 2002
Norfluoxetine	STP Influent water	0.0099 µg/l	Vanderford et al., 2006
Norfluoxetine	STP Effluent water	0.0039 µg/l	Vanderford et al., 2006
Norfluoxetine	Surface water	0.0013 µg/l	Vanderford et al., 2006
Citalopram	STP Influent water	13 – 612 µg/l	Vasskog et al., 2006
Citalopram	STP Effluent water	9.2 – 382 µg/l	Vasskog et al., 2006
Paroxetine	STP Influent water	0.0006 – 12 µg/l	Vasskog et al., 2006
Paroxetine	STP Effluent water	0.0005 – 0.0016 µg/l	Vasskog et al., 2006
Diazepam	STP Influent water	< 0.010 µg/l	Hummel et al., 2006
Diazepam	STP Influent water	< 0.0025 µg/l	Vanderford et al., 2006
Diazepam	STP Effluent water	< 0.005 µg/l	Hummel et al., 2006
Diazepam	STP Effluent water	0.0037 µg/l	Vanderford et al., 2006
Diazepam	Surface water	0.002 µg/l	Hummel et al., 2006
Diazepam	Surface water	0.0026 µg/l	Vanderford et al., 2006
Diazepam	Italian rivers	0.0002 – 0.002 µg/l	Calamari et al., 2003
Oxazepam	STP Influent water	0.86 µg/l	Hummel et al., 2006
Oxazepam	STP Effluent water	0.63 µg/l	Hummel et al., 2006
Oxazepam	Surface water	0.40 µg/l	Hummel et al., 2006
Oxazepam	German Rivers	0.013 – 0.4 µg/l	Hummel et al., 2006

## 7 Sampling programme and study sites

### 7.1 National sampling programme

A sampling strategy for the screening program was developed in order to determine the environmental concentrations of the selected pharmaceuticals in different environmental matrices in Sweden. An additional aim of the sampling programme was to identify major emission sources as well as important transport pathways. The sampling programme was based on identified possible emission sources and the behaviour of the substances in the environment. Release to water was identified as the main pathway for the pharmaceuticals entering into the environment.

STPs were identified as the most important source for the occurrence of the pharmaceuticals in the aquatic environment. Both water and sludge samples, from the STPs were included in the sampling program. Sludge from STPs is often used as indicator for diffuse spreading of chemicals to the environment.

Another depicted route of pharmaceuticals into the environment is residual medicine being added to the domestic garbage disposal system. One of the main issues in selecting appropriate sampling schemes resided in whether pharmaceuticals could be detected in landfills.

The importance of diffusive spreading of the pharmaceuticals in an urban area was investigated in Stockholm where water, sediment and biota samples were collected. Environmental background levels in water and sediment were determined in samples from three lakes located in background areas where the influence from human activities was considered minor.

The sampling program is summarised in Table 8. Site information and sample characteristics of the samples collected within the national program are given in Appendix 1.



Table 8. National sampling programme

Source	Site	Surface water	Sediment	Effluent/ leachate Water	Sludge	Biota	Total
<b>Background</b>	Lake	3	3			3	9
<b>Point sources/ Affected areas</b>	Högbytorp landfill			1			1
	Strandmossen landfill			1			1
	Fågelmyra landfill			1			1
<b>Diffuse sources</b>	Henriksdal STP, Stockholm			1	1		2
	Käppala STP			6	4		10
	Bromma STP			1	1		2
	Hammarby sjöstad			1	2		3
	Aggerud STP			1			1
	Sjöstad STP, Karlstad			1			1
	Lindesberg STP			1			1
	National reference STP				7		7
	Urban Stockholm	4	4			3	10
	Stockholm STP Effluent recipients	2	2			3	7
<b>Total</b>		<b>9</b>	<b>9</b>	<b>15</b>	<b>14</b>	<b>9</b>	<b>56</b>

## 7.2 Regional sampling programmes

Swedish county administrative boards had the possibility to add samples (70 altogether) to the national sampling programme. The main focus for the regional screening was samples from STPs. The majority of samples were taken from either effluent water (26 samples) or sludge (19 samples). Also influent water (14 samples) was collected.

In addition, leachate water from landfills (2 samples), hospital effluents (2 samples) surface water (6 samples) as well as produced drinking water (3 samples) was included in the regional programme. In total five county administrative boards participated in the regional screening programme.

Detailed information about sampling sites and sample characteristics of the samples included in the regional program are given in Appendix 2.

## 8 Methods

### 8.1 Sampling

As a guideline for adequate and consequent sampling, a manual for the sampling personnel in the national as well as the regional screening programs was developed. Detailed instructions for sampling, storing and transport were outlined. Sampling protocols for all sample types were included in the manual. The overall aim of the sampling protocols was to:

1. Guide the responsible personnel on how to avoid contamination when sampling
2. Ensure documentation of the sampling procedure, quality of the sample and environmental and physical circumstances during the sampling.

The samples from the regional county administrative boards were sent to IVL Swedish Environmental Research Institute.

#### 8.1.1 Water

Water samples were collected in cleaned plastic bottles and stored frozen until analysed. A bottle with ultra pure water (Milli-Q), which was exposed to the surrounding environment during the sampling time, was used as a field blank.

#### 8.1.2 Sediment

Sediment samples from lakes were collected by means of a Kajak sampler. The sediment core was sliced and transferred into plastic jars and stored until analysed. A plastic jar filled with diatomaceous earth (10 % water) that was exposed to the surrounding environment during the sampling time was used as field blank.

#### 8.1.3 Sludge

The staff at the different treatment plants collected the sludge samples from the anaerobic chambers. The sludge was transferred into plastic jars and stored at 4°C or -18°C until analysed. A plastic jar filled with diatomaceous earth (10 % water), which was exposed to the surrounding environment during the sampling, was used as a field blank...

## 8.2 Analysis

### 8.2.1 Extraction of water

Pre-filtered water samples were spiked with recovery standard (d5-oxazepam) and extracted onto Oasis HLB SPE cartridges. Sample volume varied between 200 and 1000 ml depending on sample type. The cartridges were washed with ultra-pure water and dried for 15 min with the aid of a vacuum pump. The analytes were eluted with a mixture of methanol and acetone (1+4) buffered at

pH 4.5 with ammonium acetate. The extracts were concentrated prior to the Liquid Chromatography-Mass Spectrometry (LC-MS) analysis.

### **8.2.2 Extraction of sediment, sludge and fish**

Samples were spiked with recovery standard (d5-oxasepam) homogenised and extracted twice with a mixture of methanol and acetonitrile (1+1) according to Ramirez et al (2007). The extracts were centrifuged and evaporated prior to LC-MS analysis.

### **8.2.3 LC-MS analysis**

Liquid chromatography was performed with an Agilent 1100 liquid chromatography system (Agilent Technologies, Waldbronn, Germany), equipped with an autosampler, a quaternary pump, an on-line degassing system and a diode array detector (UV). The compound separation was performed with a reversed phase C<sub>18</sub>-column (Atlantis dC<sub>18</sub>, 2.1 mm ID x 150 mm length, 3 µm, Waters, Milford USA) using gradient elution with a mobile phase containing ammonium acetate buffer in acetonitrile and water.

The analytical detector was a Micromass LCT orthogonal-acceleration time-of-flight (TOF) mass spectrometer (MS) equipped with a Z-spray electro spray ion source and a 4 GHz time to digital converter (TDC) (Micromass Ltd., Wythenshawe, Manchester, UK). Electro spray ionisation (ESI) was used in positive ion mode for most of the analytes (propofol and OH-ibuprofen was analysed in negative mode) and the electro spray source parameters were optimised. The data processing and instrument (HPLC/HRMS) control were performed by the MassLynx software.

## 9 Results and discussion

The results of the measurements, from both the national and regional screening, are given in Appendix 3 to 6 where the concentrations and detection limits (LODs) for the pharmaceuticals found in the different samples are shown. In chapters 9.1 - 9.4 the results are summarised and discussed according to source category. In addition to the pharmaceuticals, caffeine was analysed in all samples as an indicator of anthropogenic influence (Seiler, R.L.Z. et al., 1999).

Concentration ranges for all substances in the different matrices are summarised in Table 9 and Table 10. Light blue colour indicates at least one value above LOD, dark blue indicates all values above LOD.

Table 9. Concentration ranges in water (the number of samples analysed are within brackets)

	STP Influent (20) ng/l	STP Effluent (34) ng/l	Surface & drinking water (13), ng/l	Lechate water (4), ng/l
<b>Fentanyl</b>	<2	<2	<2	<2
Norfentanyl*	<5	<5	<5	<5
<b>Dextropropoxyphene</b>	<2	<2	<2	<2
Norpropoxyphene*	<5	<5	<5	<5
<b>Propofol</b>	<0.6 - 29	<0.6 - 510	<0.6	<0.6 - 18
<b>Bromocriptine</b>	<2	<2	<2	<2
<b>Thioridazine</b>	<2	<2	<2	<2
<b>Clozapine</b>	<3	<3	<3	<3
<b>Risperidone</b>	<1 - 20	<1 - 8	<1	<1 - 260
<b>Zolpidem</b>	<1 - 31	<1 - 14	<1	<1
<b>Sertraline</b>	<1	<1	<1	<1
<b>Fluoxetine</b>	<1 - 66	<1 - 53	<1	<1
<b>Flunitrazepam</b>	<1	<1	<1	<1
7-Aminoflunitrazepam*	<5 - 78	<5	<5	<5 - 1 000
N-Demetyflunitrazepam*	<5	<5	<5	<5
<b>Diazepam</b>	<0.8	<0.8	<0.8	<0.8
Nordiazepam*	<3 - 28	<3 - 30	<3	<3
<b>Oxazepam<sup>a</sup></b>	33 - 1 200	79 - 1 200	<4 - 24	10 - 110
<b>Zopiclone</b>	<1	<1	<1	<1
Zoplikone-N-oxide*	<5 - 230	<5 - 89	<5	<5
<b>Citalopram</b>	12 - 180	<0.3 - 120	<0.3	<0.3 - 26
<b>Paroxetine</b>	<1 - 70	<1 - 56	<1	<1 - 1 200
<b>Caffeine</b>	13 000 - 150 000	<8 - 43 000	<8 - 250	<8 - 550 000

\*metabolite of the substance above, <sup>a</sup>metabolite of diazepam but also sold as an individual pharmaceutical.

Table 10. Concentration ranges in sludge, sediment and fish (the number of samples analysed are within brackets)

	Sludge (32), ng/g dw	Sediment (9), ng/g dw	Fish (9), ng/g ww
<b>Fentanyl</b>	<1	<1	<1
Norfentanyl*	<1	<2 - 110	<2
<b>Dextropropoxyphene</b>	<0.9-1	<0.9	<0.9
Norpropoxyphene*	<1	<1	<1
<b>Propofol</b>	<0.1 - 4.5	<0.1 - 4.4	<0.1
<b>Bromocriptine</b>	<1	<1	<1
<b>Thioridazine</b>	<1	<1	<1
<b>Clozapine</b>	<0.8 - 68	<0.8	<0.8
<b>Risperidone</b>	<0.5	<0.5	<0.5
<b>Zolpidem</b>	<0.2 - 3.8	<0.2	<0.2
<b>Sertraline</b>	1.6 - 310	0.3 - 1.6	<0.3
<b>Fluoxetine</b>	<0.5	<0.5	<0.5
<b>Flunitrazepam</b>	<0.5	<0.5 - 3.3	<0.5
7-Aminoflunitrazepam*	<1	<1	<1
N-Demetyflunitrazepam*	<1	<1	<1
<b>Diazepam</b>	<0.5	<0.5	<0.5
Nordiazepam	<1	<1	<1
<b>Oxazepam<sup>a</sup></b>	<1 - 110	<1	<1
<b>Zoplikone</b>	<1	<1	<1
Zoplikone-N-oxide*	<1	<1	<1
<b>Citalopram</b>	23 - 210	<0.5 - 1.8	≤0.3 - <0.5
<b>Paroxetine</b>	<0.5	<1	<1
<b>Caffeine</b>	<2 - 560	<2	<2

\*metabolite of the substance above, <sup>a</sup>metabolite of diazepam but also sold as an individual pharmaceutical.

## 9.1 Municipal sewage treatment plants

### 9.1.1 Influent water

Oxazepam and citalopram were the most frequently found pharmaceuticals in influent water samples (Figure 3). Oxazepam occurred at several sites in significantly higher concentrations than any of the other pharmaceuticals included in this study, ranging between 33 ng/l and 1200 ng/l. The increased concentrations might not only reflect the actual consumption of oxazepam as this compound is a dominant metabolite of several other benzodiazepines. Oxazepam has earlier been measured by Hummel et.al. (2006) in a concentration of 860 ng/l which is in the same range as what has been found in this study. No other benzodiazepine was found in the influent waters. The non-benzodiazepine zolpidem was however detected in three STPs in concentrations between 17 and 31 ng/l.

The SSRI-pharmaceutical citalopram was as frequently detected as oxazepam but in lower concentrations, ranging from 12 ng/l to 180 ng/l. This is lower than what earlier has been

measured in influent water samples from STPs in Norway where concentrations up to 612 µg/l could be found (Vassskog et al., 2006).

The other SSRI-pharmaceuticals, paroxetine and fluoxetine were detected in the same concentration range as citalopram (24 ng/l - 70 ng/l and 63-66 ng/l respectively) but only in samples from five and two STPs respectively. The levels of paroxetine were lower while the levels of fluoxetine were in the same range as what has previously been measured in Norway (12000 ng/l and 2.4 ng/l respectively; Vassskog et al., 2006)

Despite being distributed only at hospitals the anaesthetic drug propofol was found in the influent water at eight different STPs in concentrations between 1.2 and 29 ng/l. The antipsychotic drug risperidone occurred at three STPs at 17 - 20 ng/l.

The metabolite of diazepam, nordiazepam, was detected in three different influent water samples in concentrations of 27 - 28 ng/l. The metabolite of flunitrazepam, 7-aminoflunitrazepam could be detected in the influent from one STP in a concentration of 78 ng/l and the metabolite of zopiclone, zopiclone -N-oxide was found in a concentration of 230 ng/l at one STP. However, none of the parent substances of these metabolites was detected in the influent water at any of the STPs.

Caffeine was detected in all samples in concentrations between 13 000 and 150 000 ng/l.

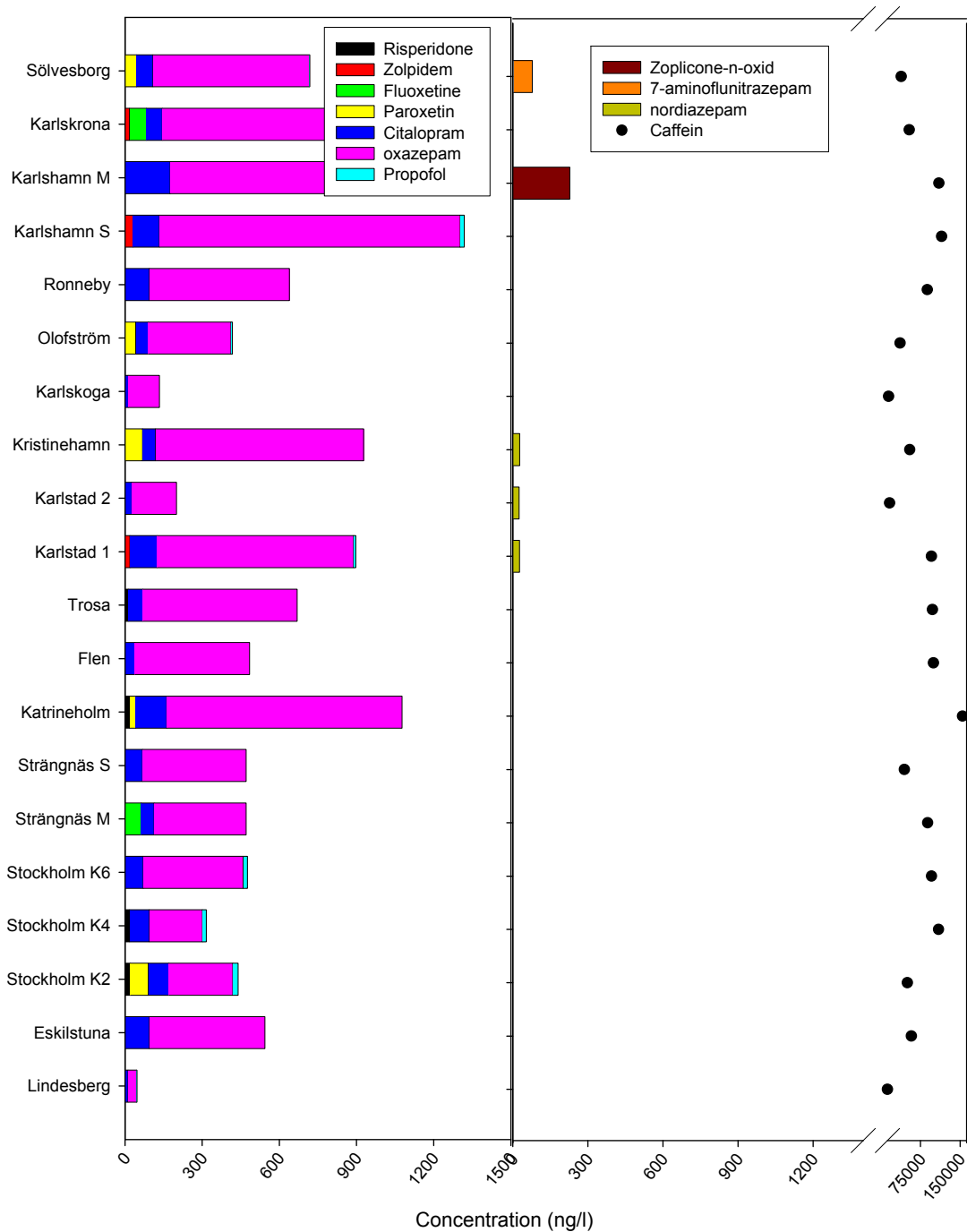


Figure 3. Concentrations of pharmaceuticals (left) and pharmaceutical metabolites + caffeine (right) in influent water from municipal STPs

Regarding the occurrence of metabolites in the influent water samples (displayed in right pane in Figure 3), nordiazepam was detected above the LOD in three samples (Kristinehamn and the two samples from Karlstad) while zopiclone-n-oxide and 7-aminoflunitrazepam occurred in one

influent sample respectively. The main reason to include caffeine as a reference substance in the study was that it can serve as an indicator of 1) anthropogenic influence; since caffeine is being consumed in vast amounts as a drug and also excreted from the consumption of coffee, and 2) of the efficiency of the STP (will be further discussed in 9.1.2). High concentrations of caffeine in the influent water samples should preferentially be accompanied with high (relatively) concentrations of the human pharmaceuticals. When analysing the resulting concentration data from the influent water samples, this correlation between caffeine concentrations and the concentration of each detected pharmaceutical, this correlation stands out as less obvious (Figure 4 and Figure 5).

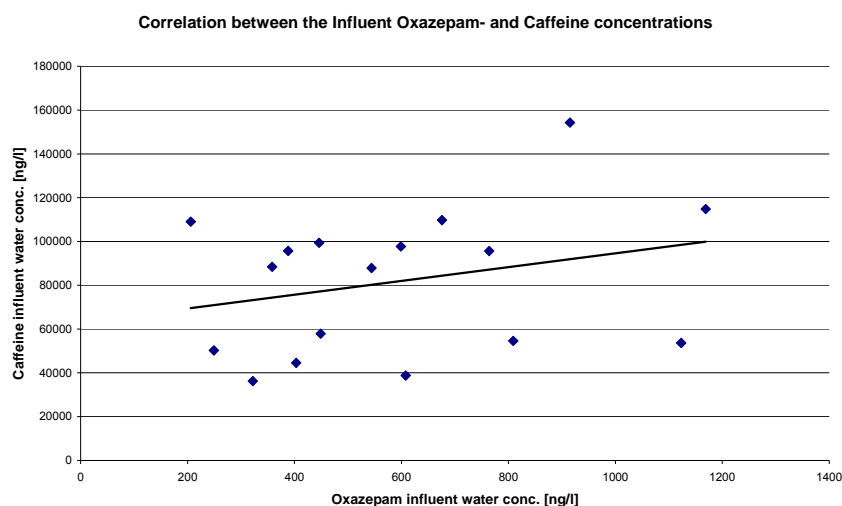


Figure 4. Correlation between influent concentrations of caffeine and oxazepam.

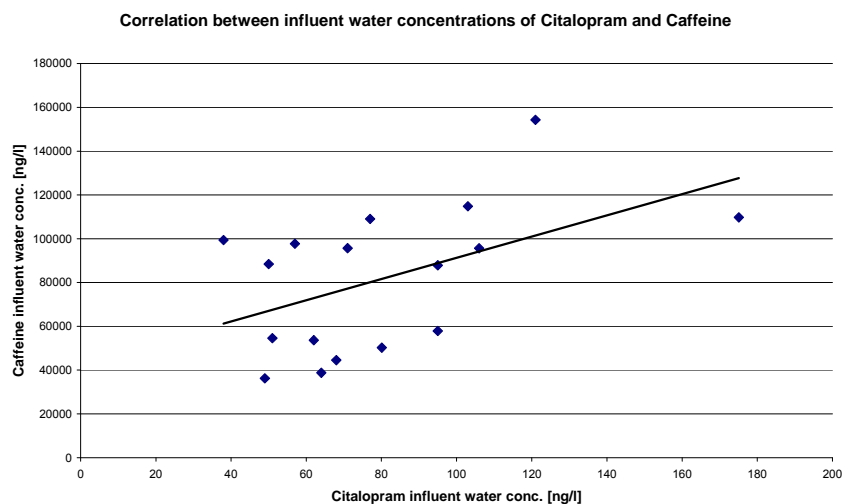


Figure 5. Correlation between influent concentrations of caffeine and citalopram.

This type of plots could easily be made for all pharmaceuticals included in the study however, the detection frequency of the other substances in influent water samples were so low that plotting their caffeine-correlation does not serve any purpose.



Another possible marker for anthropogenic influence of pharmaceutical residues is hydroxyl ibuprofen, a metabolite of the very common NSAID substance ibuprofen (*NSAID* = Non-Steroidal Anti-Inflammatory Drug). Hydroxy ibuprofen was detected above the LOD in all influent STP water samples (Figure 6).

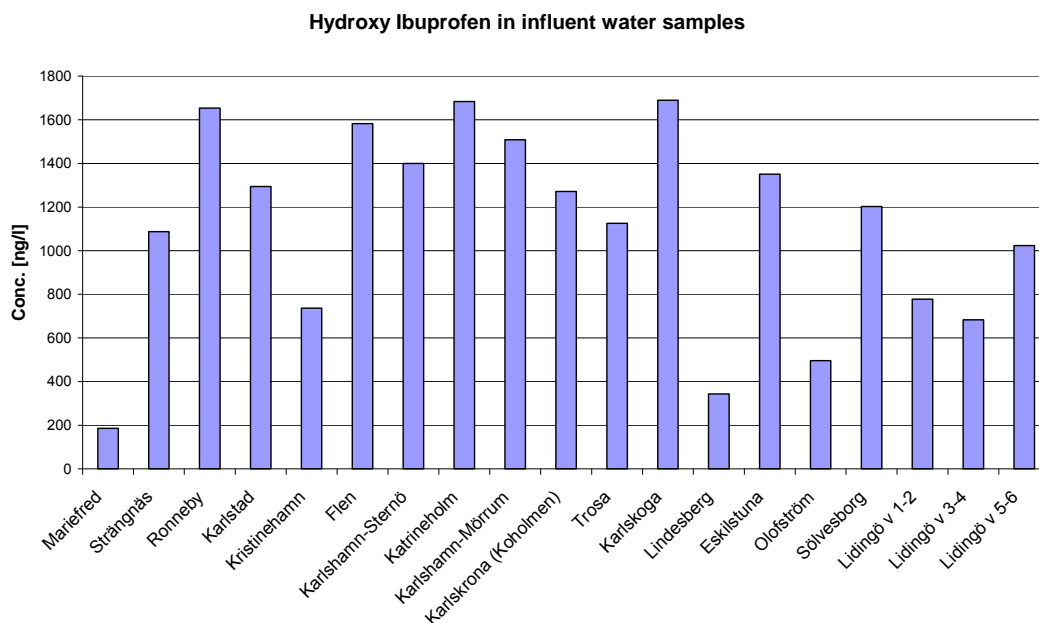


Figure 6. STP Influent concentrations of hydroxy ibuprofen.

Oxazepam concentrations in the STP influent water samples did not correlate with the corresponding hydroxyl ibuprofen concentrations (not shown), however for citalopram also hydroxyl ibuprofen can be used as a anthropogenic emission marker (Figure 7).

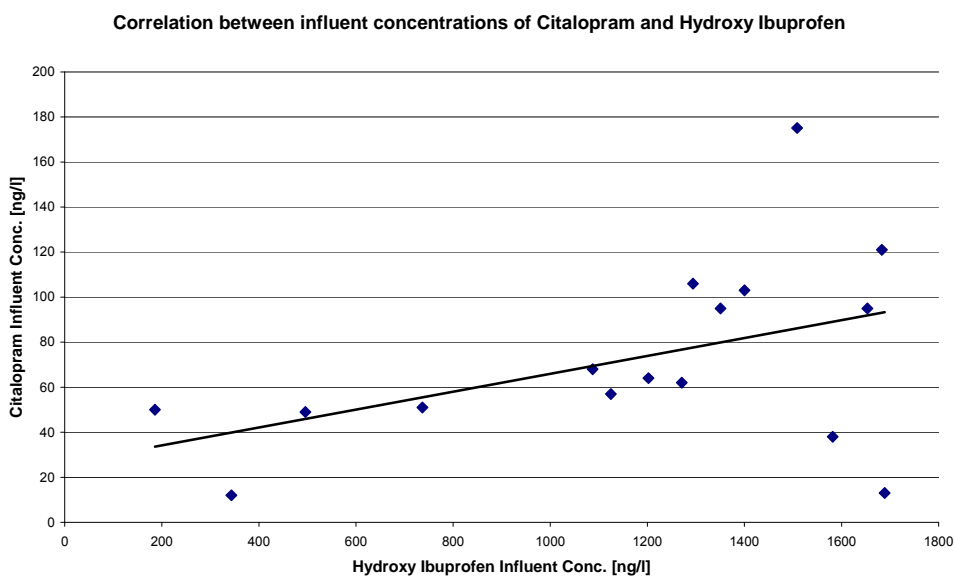


Figure 7. Correlation between influent concentrations of citalopram and hydroxy ibuprofen.

### 9.1.2 Effluent water

Oxazepam and citalopram were the most frequently detected substances also in effluent water and they were found at all STPs (Figure 8). Oxazepam was still the pharmaceutical substance that was detected in the highest concentration ranging from 200 ng/l to 1200 ng/l. At several of the STPs, the concentration of oxazepam in the effluent water exceeded the concentration in the influent water (Figure 12). The concentrations of oxazepam found in effluent water in this study were in the same range as what was measured by Hummel et al. (630 ng/l; 2006).

The non-benzodiazepine zolpidem was detected in the effluent water from six of the STPs in concentrations of 5 -14 ng/l, which were lower than what was measured in the influent water.

The SSRI-drug citalopram was detected in the effluent from all the STPs in concentrations ranging between 21 and 130 ng/l. Also citalopram was frequently found in higher concentrations in effluent water than in influent water from the same STP (Figure 12 and the "removal rate-plot" in Figure 9). This pattern was also evident for the two other SSRIs, paroxetine and fluoxetine, which were found in concentrations between 17-56 ng/l and 23 -53 ng/l. The levels of citalopram found in this study were mostly lower than what was previously measured in Norway (9.2 - 380 µg/l) while levels of paroxetine and fluoxetine were somewhat higher than what was found in Norway (1.6 and 1.3 ng/l respectively; Vasskog et al. 2006).

The anaesthetic drug propofol was found even more frequently in effluent waters (0.8 ng/l - 510 ng/l) than in the influent water with concentrations exceeding those in influent waters. The antipsychotic drug risperidone was only found in the effluent from two STPs in concentrations of 3 - 8 ng/l.

The metabolite of diazepam, nordiazepam occurred at more sites in effluent waters than in influent waters, but in the same concentration range (9 - 30 ng/l). The metabolite of flunitrazepam, 7-aminoflunitrazepam was instead detected at the same site as for influent water but in a lower concentration (26 ng/l). The metabolite of zopiclone, zopiclone-N-oxide was only found in the effluent from one of the STPs, however this was not at the same STP where it was found in influent water. None of the parent substances of these metabolites could be detected in the effluent waters.

Caffeine was detected in all samples except for six STPs however in much lower concentrations (92 to 44 000 ng/l) than in the influent waters. Also hydroxyl ibuprofen was frequently detected (20 effluent water samples out of 30), and the concentration ranged between <6 ng/l to 1700 ng/l (Figure 11).

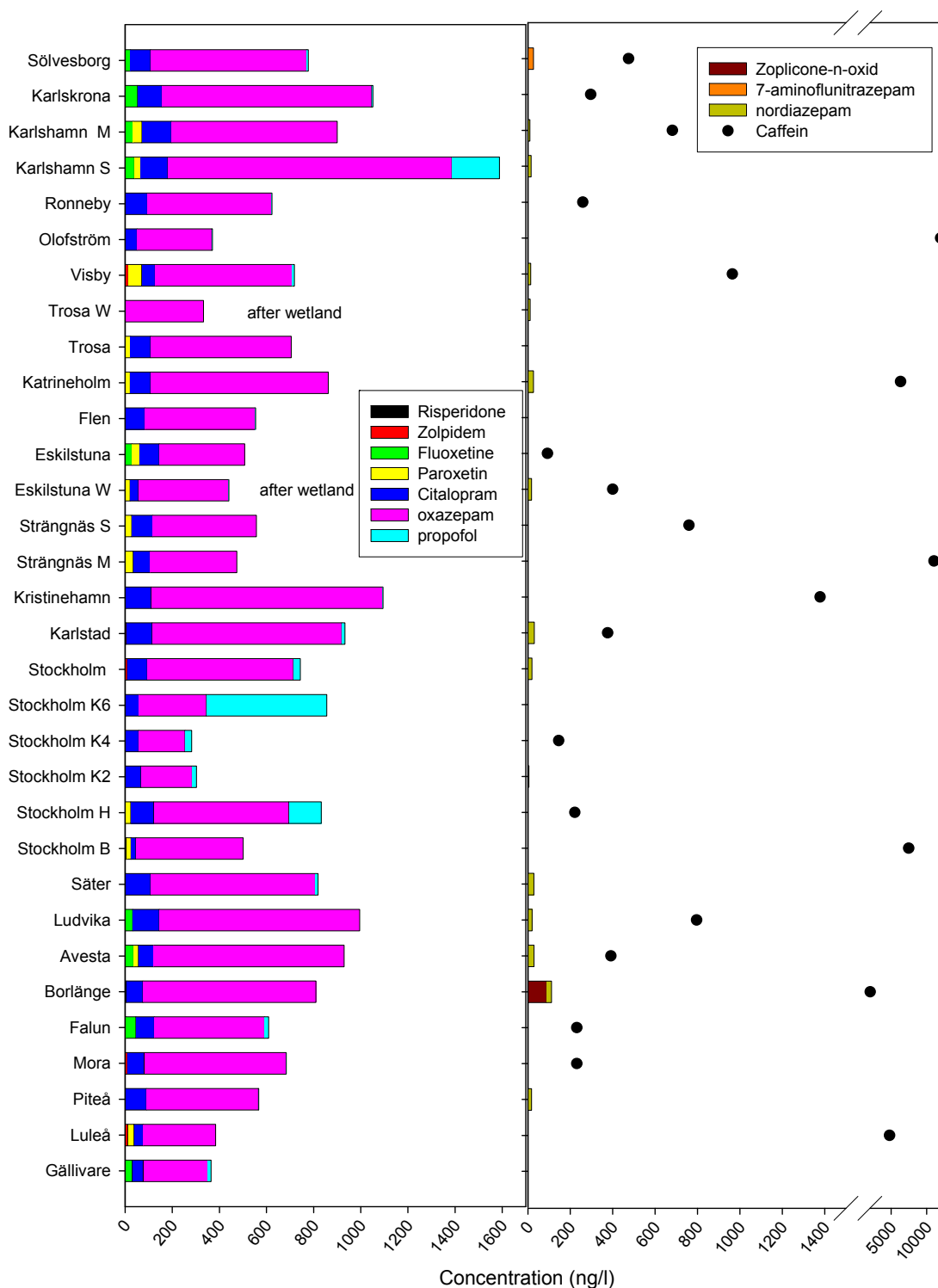


Figure 8 . Concentrations of pharmaceuticals (left pane) and pharmaceutical metabolites (right pane) in effluent water from municipal STPs sorted from south to north.

In 17 of the STPs the sampling programme allows for a simple assessment of the removal efficiency of the STP, i.e., the removal rate. Caffeine can be expected to be rather easily removed in the STPs (having long enough hydraulic retention times) since it is rather polar, it is not excreted as glucuronides, and seems to be easily incorporated in the metabolism of micro organisms (Seiler, R.L.Z. et al., 1999 and Ogunseitan O.A, 1996). Removal rates of 85-98 % have previously been reported regarding caffeine (Ternes et al., 2006 and Heberer et al., 2002). When removal rates of the most frequently detected pharmaceuticals in the effluent water samples in the present study (oxazepam and citalopram) are plotted together with the corresponding removal rates of caffeine, it seems likely that extensive re-formation of active pharmaceutical substance occurs especially for citalopram (Figure 9). In fact, the STP-passage seems only to affect the aqueous water concentration of oxazepam and citalopram to a minor extent.

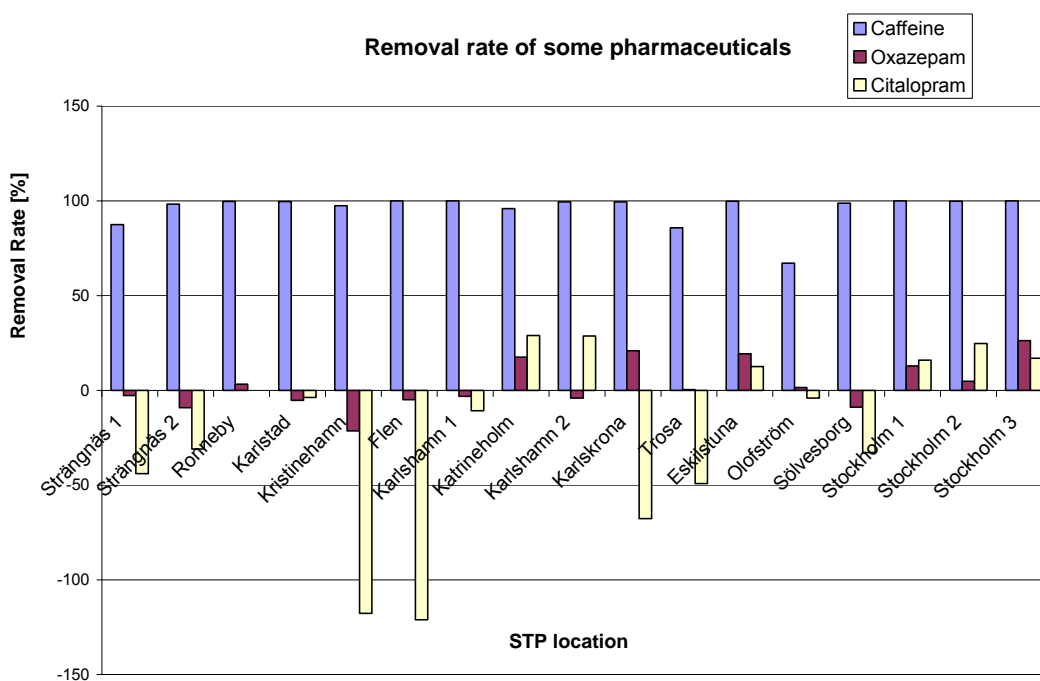


Figure 9. Removal rates from 17 STPs (influent- and effluent data) for caffeine, oxazepam and citalopram.

Peculiarity with effluent data displayed in Figure 8 is the fact that the intravenously administered anesthetic propofol has been detected in 19 effluent samples. Propofol is hydrophobic and rather volatile low molecular weight molecule. It is thus less probable to end up in the effluent water. De-glucuronidation could possibly explain this finding.

Nordiazepam (the de-methylated form of diazepam is the metabolite most frequently detected in the effluent water samples. This is somewhat surprising considering the fact that only 170 kg of the mother compound, diazepam, was sold during 2006 in Sweden. Nordiazepam is but one of several metabolites of diazepam.

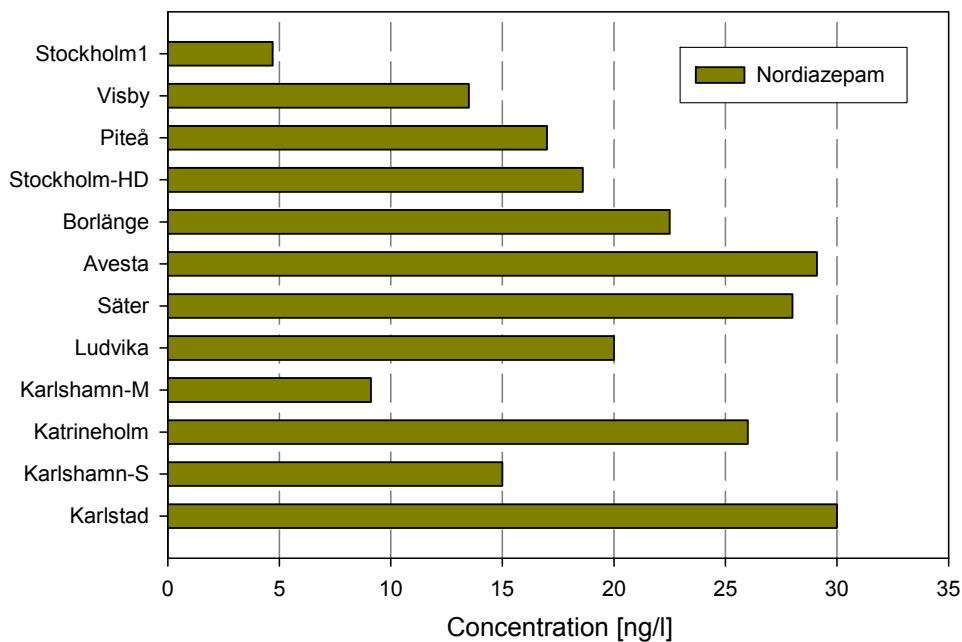


Figure 10. Effluent concentrations of the metabolite nordiazepam (the most frequently encountered metabolite in the effluent water samples).

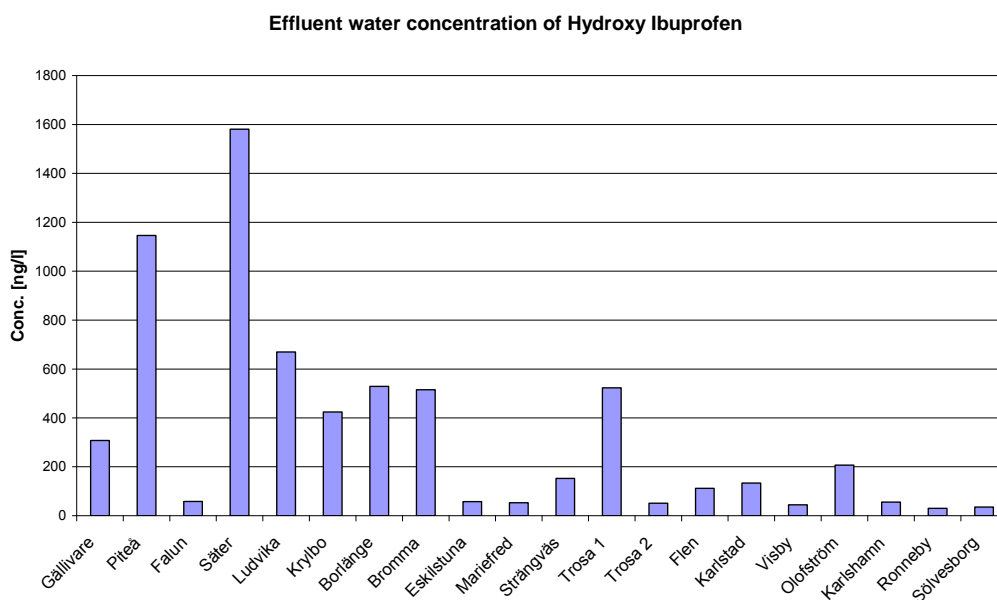


Figure 11. Effluent water concentrations of hydroxy ibuprofen, STPs sorted approximately from north to south.

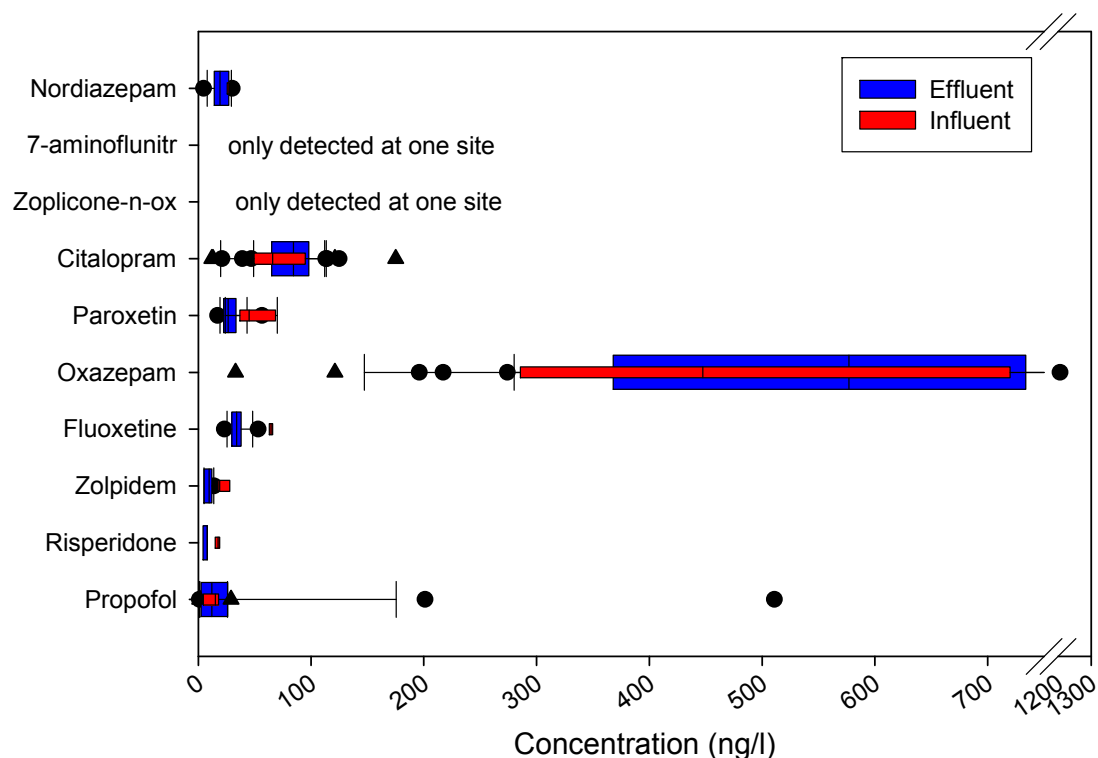


Figure 12. Influent and effluent sewage water (20 influent samples, 30 effluent samples). The lower and upper boundaries of the box represent the 25- and 75-percentiles, the line within the box is the median concentration. The whiskers represent the 10- and 90- percentiles, and the dots (effluent) and triangles (influent) are individual results outside this range. Re-transformation of the mother substances back from glucuronidated- and sulfonated metabolites can explain the fact that effluent concentrations occasionally are higher than the corresponding influent concentrations.

### 9.1.3 Sludge

The SSRI-drugs sertraline and citalopram were detected in all sludge samples in concentrations of 8 - 300 ng/g dw and 23 - 210 ng/g dw respectively (Figure 13). No other SSRI-drugs could be detected in the sludge samples.

The drug dextropropoxyphene was detected in one of the sludge samples. The concentration (1 ng/g dw) was however close to the detection limit (0.9 ng/g dw).

Oxazepam occurred less frequently in sludge compared to the water samples and in concentrations between 14 ng/g dw and 110 ng/g dw. No other metabolites were detected in sludge. Metabolites are in general more water soluble than the mother substances and less prone to end up in the solid phase, which could serve as explanation.

The non-benzodiazepine zolpidem and anti-psychotic drug clozapine were detected less frequently than the other substances and in somewhat lower concentrations, 1.2 - 3.8 ng/g dw and 3.8 - 68 ng/g dw respectively.

The anaesthetic drug propofol occurred even more scarcely and in even lower concentrations, 0.2 - 0.3 ng/g dw. Caffeine was only found in 5 sludge samples.

Hydroxy ibuprofen was, as expected from theoretical considerations of fate, not detected very frequently in the sludge samples (in 5 samples out of 36). It is more hydrophilic and polar than the mother compound ibuprofen, which is well known to predominate in the aqueous phase of the sewage (Figure 14).

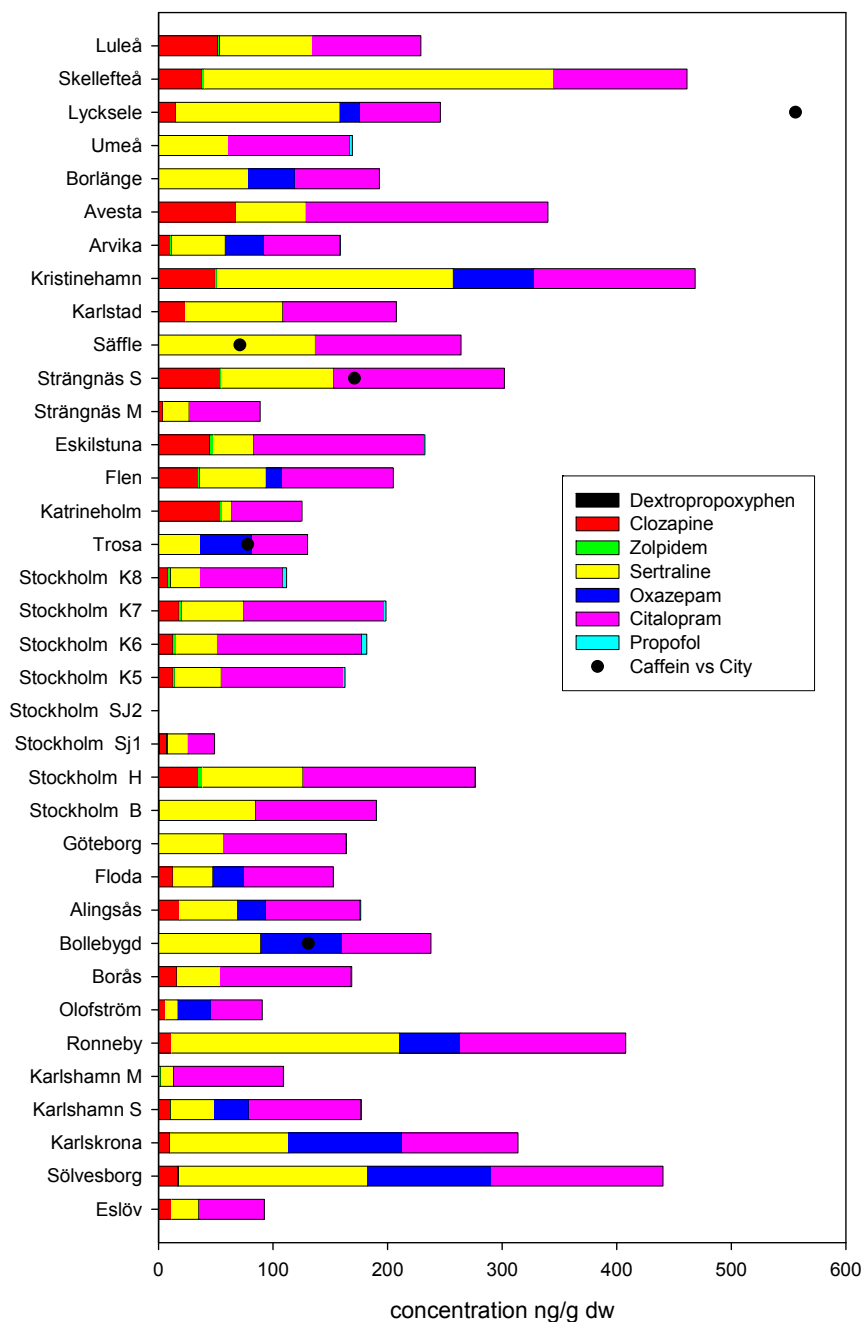


Figure 13 Concentrations of pharmaceuticals and pharmaceutical metabolites in sludge from municipal STPs

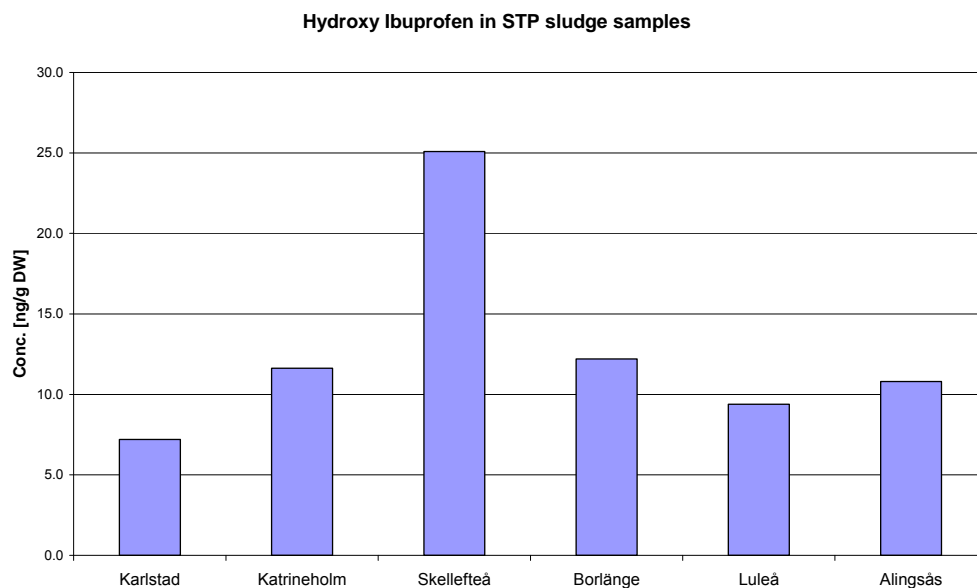


Figure 14. Hydroxy ibuprofen detected in STP sludge samples.

## 9.2 Point sources

### 9.2.1 Effluent water from hospitals

Oxazepam was like in the water samples from the STPs the dominating substance in the two hospital effluent waters (Table 11). Citalopram was only detected in the sample from Karlskrona while propofol was detected in both samples. The concentrations were in the same range as in effluent waters from STPs.

Table 11. Pharmaceuticals detected in hospital effluents.

All concs. in [ng/l]	Propofol	Oxazepam	Citalopram	OH-Ibuprofen	Caffeine
Karlskrona hospital	7.4	240	<0.3	115	150 000
Karlshamns hospital	98	79	49	104	110 000

## 9.3 Municipal landfills

Five municipal landfills were included in the study. There was a large variation in the distribution as well as in the concentrations of the pharmaceuticals in the different leakage water samples (Table 12). Oxazepam was detected in all samples in concentrations ranging between 10 and 110 ng/l. At Borlänge landfill risperidone occurred in a concentration of 260 ng/l and citalopram in a concentration of 26 ng/l. At Bro landfill paroxetine was found in a concentration of 1200 ng/l,



propofol in a concentration of 18 ng/l and the metabolite 7-aminoflunitrazepam in a concentration of 1000 ng/l. Hydroxy ibuprofen was below LOD in all of the leachate water samples.

Table 12. Pharmaceuticals and pharmaceutical metabolites detected in leachate water from municipal landfills.

All concs. in [ng/l]	Propofol	Risperidone	Oxazepam	Paroxetine	Citalopram	7-aminoflunitrazepam	Caffeine
Borlänge 2	<0.6	<1	24	<1	<0.3	<5	824
Standmossen	<0.6	<1	9.6	<1	<0.3	<5	590
Bro	18	<1	24	1200	<0.3	1030	370 000
Borlänge 1	<0.6	260	12	<1	26	<5	550 000
Karlskrona	<0.6	<1	110	<1	<0.3	<5	<8

## 9.4 Environmental concentrations

### 9.4.1 Surface- and drinking water

Oxazepam was the only pharmaceutical drug found in surface water samples. It was detected in all samples except one in concentrations between 9 and 24 ng/l (Figure 15). The concentrations were about a factor of ten lower compared to the effluent water samples from STPs. No significant difference was found between sample taken near the outlets of STPs and the other urban water samples. The levels of oxazepam were lower than what has been reported by Hummel et.al. (400 ng/l; 2006). Caffeine was found in all the samples where oxazepam was detected indicating that presence of this pharmaceutical is related to human consumption.

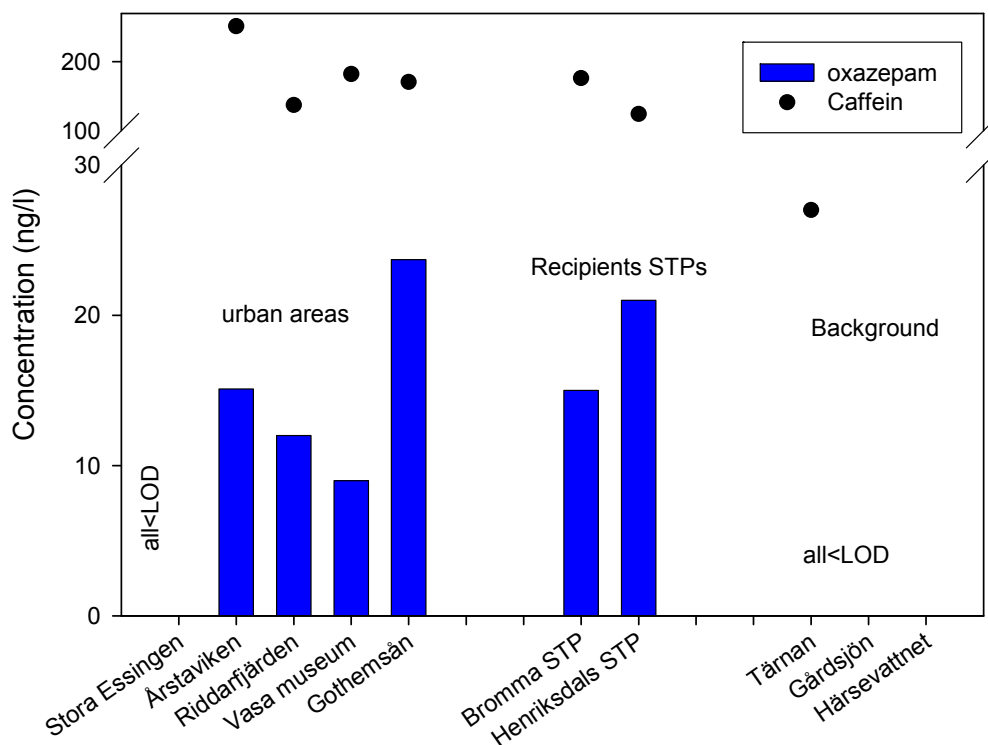


Figure 15. Concentrations of oxazepam and caffeine in surface waters

None of the incoming surface water samples to water works contained any of the included pharmaceuticals in concentrations above the LOD. Neither did the produced drinking water samples.

Hydroxy ibuprofen was not detected in neither the surface water samples or in the drinking water samples. A more concise tabulation of LODs for the pharmaceuticals in different water matrices is given in Table 13 and Table 14.

Table 13. Summary of detection limits (ng/l) in different water matrices.

Matrix	Propofol	Fentanyl	D-pro-poxy-phene	Bromo-criptine	Thio-ridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitra-zepam	Oxa-zepam
Influent water	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1	<4
Effluent water	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1	<4
Leachate water	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1	<4
Surface water	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1	<4

Table 14. Summary of LODs (ng/l) in different water matrices (continued).

Matrix	Dia-zepam	Paroxetine	Citalopram	Zopiclon	N-pro-poxy-phene	N-fentanyl	Zopiclon-N-oxide	N-demethyl-flunitra-zepam	7-amino-flunitra-zepam	Nordia-zepam	Caffeine	Hydroxy-ibu-profen
Influent water	<0.8	<1	<0.3	<1	<5	<5	<5	<5	<5	<3	<8	<6
Effluent water	<0.8	<1	<0.3	<1	<5	<5	<5	<5	<5	<3	<8	<6
Leachate water	<0.8	<1	<0.3	<1	<5	<5	<5	<5	<5	<3	<8	<6
Surface water	<0.8	<1	<0.3	<1	<5	<5	<5	<5	<5	<3	<8	<6

## 9.4.2 Sediment

Oxazepam was not detected in any of the sediment samples. Instead citalopram was the most frequently occurring substance in this type of matrix, found in concentrations between 0.8 and 1.8 ng/g dw (Figure 16). In the background sample from Lake Lilla Öresjön flunitrazepam was surprisingly detected in a concentration of 3.3 ng/g dw. Also caffeine was also found in this sample and in addition, our previous screening investigation on human pharmaceuticals also showed presence of other pharmaceuticals in samples from this particular background lake (Andersson et al., 2006). The origin of these substances is probably from private sewage systems belonging to summer cottages situated around the lake. Flunitrazepam was found in one sediment sample from Stockholm and in a sample collected close to a for STPs in concentrations of 0.9 ng/g dw and 0.6 ng/g dw respectively.

In Stockholm, in the water outside the Vasa museum, at a site representing urban influence, sertraline was found in a concentration of 1.6 ng/g dw in sediment, while propofol was detected in a sediment sampled near the outlet from Bromma STP (Saltsjön) in a concentration of 4.4 ng/g dw. As mentioned previously, it is rather surprising to detect propofol in this type of sample. Considering the low molecular weight and 'high' vapour pressure of propofol, the substance is from a theoretical point of view more likely to be vented of in the biological steps of the STP (Figure 16). Hydroxy ibuprofen was not detected in any of the sediment samples (LOD <6 ng/g dw).

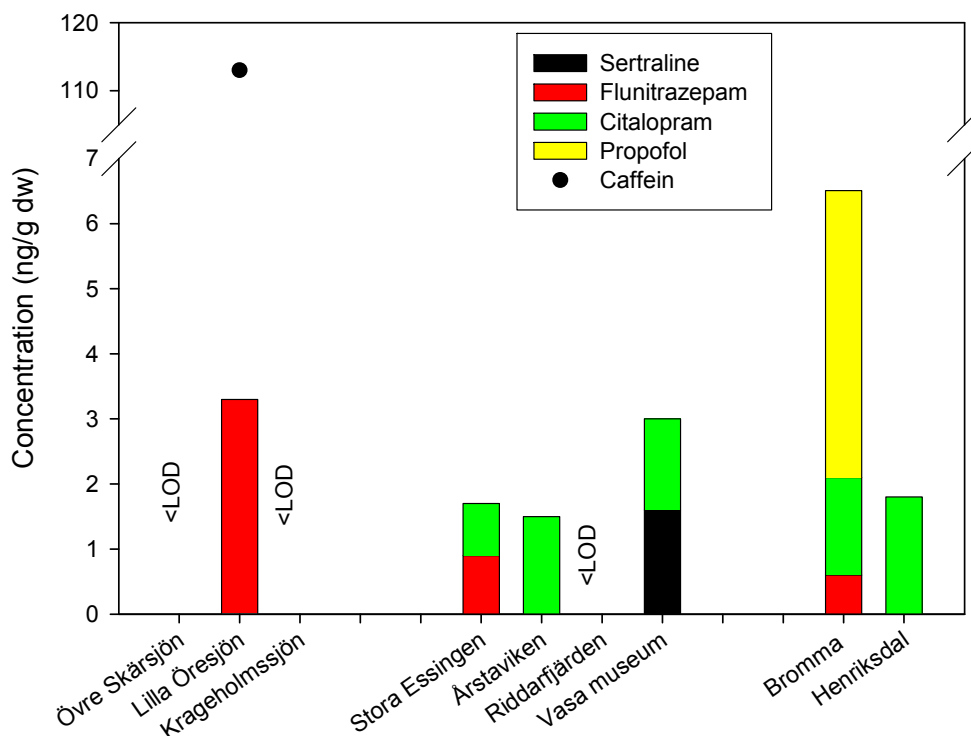


Figure 16. Concentrations of pharmaceuticals and pharmaceutical metabolites in sediment

### 9.4.3 Fish

The fish sample from Riddarfjärden, Stockholm area, contained trace amounts of citalopram,  $\leq 0.3$  ng/g ww. However this concentration is close to the detection limit of the analytical method and the result should be interpreted with some caution and be seen as an indication that this substance may end up in biota. The LOD obtained for citalopram for other fish samples was 0.5 ng/g ww. The concentrations of the other pharmaceuticals were below LOD in the biota samples from the Stockholm area.

None of the pharmaceutical analytes were detected in any of the background samples (see appendix 5 and 6 for detailed information on LODs).

## 9.5 Risk assessment (MEC/PNEC)

A way to relate the measured concentrations to known environmental effects is to perform a risk assessment and derive risk characterisation quotients based on the measured concentrations (MEC) or predicted environmental concentrations (PEC), and the predicted no effect concentrations (PNEC). According to the guideline for environmental risk classification for *fass.se* the result of the MEC/PNEC give risk classifications according to Table 15.

Table 15. Classification system according to guidelines at fass.se

Risk quotients	Classification phrase
PEC/PNEC $\leq$ 0.1	Use of the medicine has been considered to result in <b>insignificant</b> environmental risk
0.1 < PEC/PNEC $\leq$ 1	<b>low</b> environmental risk
1 < PEC/PNEC $\leq$ 10	<b>moderate</b> environmental risk
PEC/PNEC >10	<b>high</b> environmental risk

The PNECs used for the risk assessment are given in Table 5 (Chapter 4.1). For STP-effluent waters where no recipient water samples were analysed, a dilution factor of 10 was applied to all effluent concentrations (TGD, 2003). The PNEC calculation is associated with certain uncertainties depending on availability and quality of the ecotoxicological data as well as the applied safety factors. Furthermore, the screening results (basis of the MEC-numbers) are not statistically reliable but rather “a snap shot” of the situation, thus the results of the MEC/PNEC-risk assessments should be interpreted with a bit of caution and be regarded as indications of whether there is a need for further investigations.

PNECs could only be derived for the SSRIs fluoxetine, paroxetine and citalopram as no ecotoxicity data was found for the other detected substances. The risk estimates for all those substances resulted in an “insignificant environmental risk” according to Table 16.

All MEC/PNECs gave risk quotients lower than the predicted quotients according to fass.se.

Table 16. Risk quotients and risk classifications

Pharmaceutical	MEC/PNEC	PEC/PNEC (fass.se)	Classification phrase
Fluoxetine	0.02-0.04	0.14-0.4	Use of the medicine has been considered to result in <b>insignificant</b> environmental risk
Paroxetine	0.001-0.004	0.025	Use of the medicine has been considered to result in <b>insignificant</b> environmental risk
Citalopram	0.0004-0.002	0.049	Use of the medicine has been considered to result in <b>insignificant</b> environmental risk

No ecotoxicity data was found for oxazepam, the most frequently detected pharmaceutical. In order to allow for a preliminary risk assessment a read across of the ecotoxicity data for the pharmaceutical diazepam, a structural analogue, was made. With these data risk quotients are between 0.0006 and 0.009, which gives the risk classification phrase “Use of the medicine has been considered to result in **insignificant** environmental risk.”

## 10 Conclusions

The detection frequencies for the different pharmaceutical substances investigated in this study are shown together with the current sales data in Figure 17. There is a general tendency that the most sold substances are detected most frequently. An exception is dextropropoxyphene, the second most sold substance that was detected in one sample only.

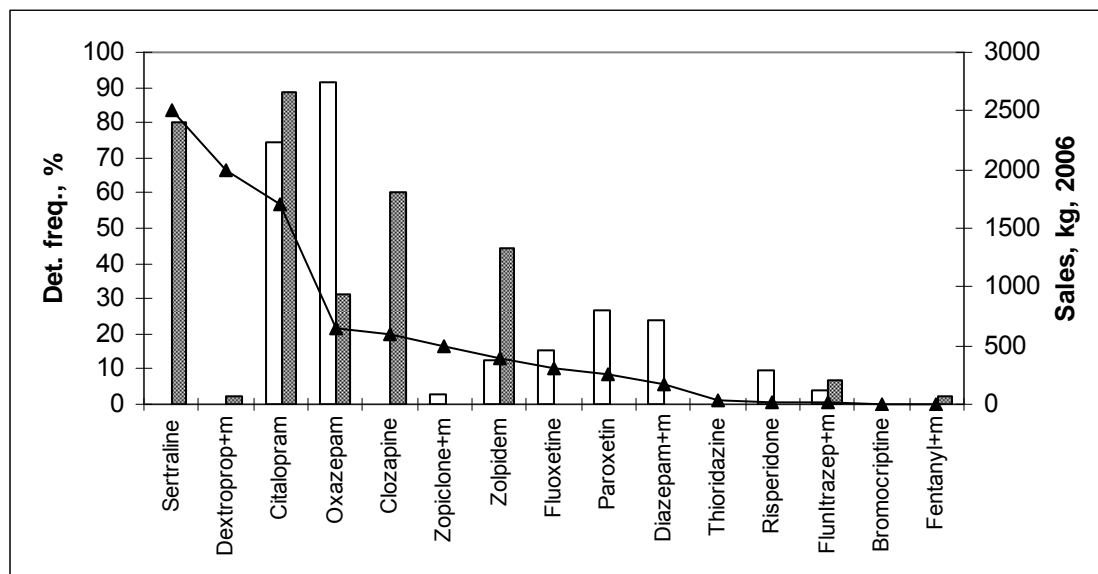


Figure 17. Detection frequency in water (white bars) and in sludge and sediment (grey bars) for the different substances (metabolites included, *i.e.*, sales figures of diazepam and detection frequency of the metabolite nordiazepam). Substances ordered by sales in 2006 (triangles). Propofol was detected in 45% of the water samples and 38% of sludge and sediment but is not shown due to lack of sales data.

Oxazepam was the most frequently detected substance as well as the substance being found in the highest concentrations in sewage water samples. Furthermore, it was the only substance being detected in surface water samples. This can not entirely be explained by its sales volume (640 kg). Another factor that has to be considered is the tendency for other benzodiazepines to metabolise into this substance. Oxazepam has a rather low log Kow of 2.2 but was nevertheless also detected STP sludge.

Risperidone on the other hand, is sold in minor quantities in Sweden (8-20 kg) but is still detected in both influent and effluent waters. However, despite having a log Kow of 3.49, risperidone was not detected in sludge. Thus, no clear correlation between sales volumes and concentrations in sewage water was identified in this study.

Factors such as degradation and the tendency to adsorb to sludge seem to influence the fate of the substances but no clear correlation between lipophilicity and the tendency to end up in sewage effluent can be drawn from these results. Factors such as the adsorption to solid matter; chelation, ionic interaction and chemisorption must also be considered to get a better understanding of the partitioning behaviour of pharmaceuticals.

Among the three substances with the highest sales volumes, sertraline, dextropropoxyphene and citalopram, only citalopram could be detected in the sewage water samples. None of the substances were detected in surface water.

Considering both aqueous and solid matrices citalopram is the most frequently encountered pharmaceutical in this study. Sertraline was however found in the highest concentrations in sludge and also has one of the highest log Kow (5.29) among the pharmaceuticals in this study. Citalopram, with a log Kow of 3.74, was also frequently found in sludge while dextropropoxyphene, with a log Kow of 4.18, was only detected once in sludge and then in a

concentration close to the detection limit. Citalopram was detected in several sediment samples while sertraline was only detected in one sediment sample.

Fentanyl, bromocriptine, thioridazine, diazepam and zopiclone were not found in any of the samples. Paroxetine was only detected in a leachate water sample while flunitrazepam were only detected in sediment samples. Fluoxetine was detected in sewage water similarly to sertraline, while zolpidem was detected in both sewage water and sludge. Clozapine was only detected in sludge.

At the *fass.se* website all pharmaceuticals are also classified according to their persistence. However, the persistence of the *fass*-classification is divided into only three classes ('degraded in the environment', 'slowly degraded in the environment', and 'potentially persistent') and it is thus difficult to draw any conclusions on the persistence of the substances included in this study with respect to their presence in Swedish STPs. Also, there is a general lack of data regarding many of the substances.

Among the metabolites, zopiclone-n-oxide (metabolite of zopiclone), 7-aminoflunitrazepam (metabolite of flunitrazepam) and nordiazepam (metabolite of diazepam) were detected in water samples. Norfentanyl (metabolite of fentanyl) was detected in sludge.

Caffeine was introduced to the sampling scheme as an indicator for human influence. Caffeine was subsequently found in all environmental water samples where pharmaceuticals were detected. In the background lake lilla Öresjön, where no pharmaceutical residues were expected to be found, the substance flunitrazepam along with caffeine was detected indicating a release of sewage water from houses not affiliated to any municipal sewage treatment plant.

Another marker for anthropogenic sources applicable when investigating pharmaceuticals is hydroxyl ibuprofen (metabolite of ibuprofen). Hydroxy ibuprofen was detected in all STP influent water samples and was also frequently encountered in the effluent water samples. Both caffeine- and hydroxy ibuprofen concentrations in influent water samples showed a slight correlation ( $r^2 = 0.25-0.35$ ) with the corresponding citalopram- and oxazepam concentrations.

The calculated removal rate of caffeine in the STPs was close to 100 %. Both oxazepam and citalopram showed low removal rates, and in some cases even negative removal rates which may indicate re-transformation from conjugated forms.

In a previously published screening report on pharmaceuticals in the Swedish environment, a correlation was identified between the detected effluent concentration of certain NSAIDs (ibuprofen and ketoprofen) and the geographic position of the STP (Andersson et al., 2006). The limited data of hydroxyl ibuprofen effluent concentrations in this study corroborate that finding.

Available ecotoxicity data lead to insignificant risk quotients for fluoxetine, paroxetine and citalopram. Furthermore, the read-across based risk quotient of oxazepam corresponds to an insignificant environmental risk also for that substance. However, it is important to keep in mind that no ecotoxicological data was found for oxazepam and risk assessment is based on data for diazepam.

For the other substances found in water effluent; paroxetine, zolpidem, risperidone and propofol no ecotoxicity data was found in the literature and hence no risk assessment could be made regarding these substances.



A recommendation for further environmental surveillance is to focus on oxazepam and citalopram; frequently found in surface water, and sertraline, citalopram, flunitrazepam and propofol that were frequently detected in solid matrices (sludge and sediments).

## 11 Acknowledgement

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**Appendix 1. Sample information national samples**

County	City	Site	Matrix	Information	Coordinates	Sample date	DW. %	Sample ID
Background		Krageholmssjön	Fish	perch		2006-10-30		5243
Background		Lilla Öresjön	Fish	perch		2006-10-31		5244
Background		Övre Skärsjön	Fish	perch		2006-10-31		5245
Background		Övre Skärsjön	Sediment			2006-11-23	11.1	5240
Background		Lilla Öresjön	Sediment			2006-11-23	5.3	5241
Background		Krageholmssjön	Sediment			2006-11-23	6.5	5242
Background		Tärnan	Water	Surface water			-	5563
Background		Gårdsjön	Water	Surface water		2007-04-11	-	5642
Background		Härsevattnet	Water	Surface water		2007-04-11	-	5643
Diffuse	Stockholm	Riddarfjärden	Fish	perch		2007-02-21		5526
Diffuse	Stockholm	Stora Essingen	Fish	perch		2007-02-22		5527
Diffuse	Stockholm	Årstaviken	Fish	perch		2007-02-23		5528
Diffuse	Stockholm	Henriksdahls STP	Fish	perch		2007-02-21		5529
Diffuse	Stockholm	Bromma STP	Fish	perch		2007-02-21		5530
Diffuse	Stockholm	Vasamuseum	Fish	perch		2007-02-21		5531
Diffuse	Stockholm	Stora Essingen	Sediment	27,7 m	5679263, 1623628	2006-12-05	14.1	5287
Diffuse	Stockholm	Årstaviken	Sediment	7,6 m	6578157, 1628321	2006-12-05	13.5	5288
Diffuse	Stockholm	Riddarfjärden	Sediment	19,2 m	6580155, 1627284	2006-12-05	15.7	5296
Diffuse	Stockholm	outside Bromma STP	Sediment				53.7	5297
Diffuse	Stockholm	outside Henriksdals STP	Sediment				38.4	5298
Diffuse	Stockholm	Vasa museum	Sediment				69.2	5502
Diffuse	Stockholm	Bromma	Sludge					5073
Diffuse	Stockholm	Henriksdal Sickla	Sludge				51.8	5075
Diffuse	Stockholm	Hammarby Sjöstad SL1	Sludge				39.3	5078
Diffuse	Stockholm	Hammarby Sjöstad SL2	Sludge					5079
Diffuse	Umeå	Umeå STP	Sludge					5220
Diffuse	Göteborg	Ryaverket STP	Sludge	605 000 p e			27.2	5221
Diffuse	Floda	Floda STP	Sludge	9 800 p e		2006	18.3	5222

County	City	Site	Matrix	Information	Coordinates	Sample date	DW. %	Sample ID
Diffuse	Alingsås	Nolhaga STP	Sludge	24 000 p e		2006	22.3	5223
Diffuse	Bollebygd	Bollebygd STP	Sludge	2 200 p e		2006	15.6	5225
Diffuse	Eslöv	Ellinge STP	Sludge	126 000 p e		2006	16.5	5226
Diffuse	Borås	Gässlösa STP	Sludge	110 000 p e		2006		5227
Diffuse	Stockholm	Käppala STP	Sludge	w. 5				5505
Diffuse	Stockholm	Käppala STP	Sludge	w. 6				5506
Diffuse	Stockholm	Käppala STP	Sludge	w. 7				5507
Diffuse	Stockholm	Käppala STP	Sludge	w. 8				5508
Diffuse	Karlstad	Sjöstad STP	Water	Influent			-	4986
Diffuse	Karlskoga	Aggerud STP	Water	Influent			-	5066
Diffuse	Stockholm	Bromma	Water				-	5072
Diffuse	Stockholm	Henriksdal Sickla	Water	effluent			-	5074
Diffuse	Stockholm	Hammarby Sjöstad	Water				-	5076
Diffuse	Lindesberg	Lindesberg STP	Water	Influent		2006	27.2	5121
Diffuse	Stockholm	Stora Essingen	Water	Surface water			-	5290
Diffuse	Stockholm	Årstaviken	Water	Surface water			-	5291
Diffuse	Stockholm	Riddarfjärden	Water	Surface water			-	5293
Diffuse	Stockholm	outside Bromma STP	Water	Surface water			-	5294
Diffuse	Stockholm	outside Henriksdals STP	Water	Surface water			-	5295
Diffuse	Stockholm	Vasa museum	Water	Surface water			-	5501
Diffuse	Stockholm	Käppala	Water	Influent w. 1-2		w. 1-2, 2007	-	5509
Diffuse	Stockholm	Käppala	Water	Effluent w. 1-2		w. 1-2, 2007	-	5510
Diffuse	Stockholm	Käppala	Water	Influent w. 3-4		w. 3-4, 2007	-	5511
Diffuse	Stockholm	Käppala	Water	Effluent w. 3-4		w. 3-4, 2007	-	5512
Diffuse	Stockholm	Käppala	Water	Influent w. 5-6		w. 5-6, 2007	-	5513
Diffuse	Stockholm	Käppala	Water	Effluent w. 5-6		w. 5-6, 2007	-	5514
Pot. point source	Bro	Högbytorp landfill	Water	Leachatewater		2007-02-13	-	5475
Pot. point source	Kristinehamn	Strandmossen landfill	Water	Leachatewater			-	5481
Pot. point source	Borlänge	Fågelmýra landfill	Water	Leachatewater			-	5538

**Appendix 2. Sample information regional samples**

County	City	Site	Matrix	Information	Coordinates	Sample date	DW. %	Sample ID
Blekinge	Ronneby	Kärragårdens water purification plant	Water	Incoming surface water (Listerån)		060916	-	4978
Blekinge	Ronneby	Kärragårdens water purification plant	Water	Drinking water		060916	-	4979
Blekinge	Ronneby	Rustorps STP	Water	Influent		060916	-	4981
Blekinge	Ronneby	Rustorps STP	Water	Effluent		060916	-	4982
Blekinge	Ronneby	Rustorps STP	Sludge			060916	46.0	4983
Blekinge	Karlshamn	Sternö STP	Water	Influent		060921-22	-	5021
Blekinge	Karlshamn	Sternö STP	Water	Effluent		060921-22	-	5022
Blekinge	Karlshamn	Sternö STP	Sludge			060922		5024
Blekinge	Karlshamn	Mörrums STP	Water	Influent		060926	-	5031
Blekinge	Karlshamn	Mörrums STP	Water	Effluent		060926	-	5032
Blekinge	Karlshamn	Mörrums STP	Sludge			060926		5034
Blekinge	Karlskrona	Bubbetorp landfill	Water	Leachatewater			-	5041
Blekinge	Karlskrona	Koholmen STP	Water	Influent		061003-04	-	5042
Blekinge	Karlskrona	Koholmen STP	Water	Effluent		061003-04	-	5043
Blekinge	Karlskrona	Koholmen STP	Sludge			061004	35.3	5044
Blekinge	Karlskrona	Lyckeby water purification plant	Water	incoming surface water (Lyckebyån)		061004	-	5046
Blekinge	Karlskrona	Lyckeby water purification plant	Water	Outgoing drinkig water		061004	-	5047
Blekinge	Karlshamn	Karlshamns water purification plant	Water	Incoming surface water (Mieån)		060926	-	5054
Blekinge	Karlshamn	Karlshamns water purification plant	Water	Drinking water		060926	-	5056
Blekinge	Olofström	Jämshögs STP	Water	Influent		061122	-	5246
Blekinge	Olofström	Jämshögs STP	Water	Effluent		061122	-	5247
Blekinge	Olofström	Jämshögs STP	Sludge			061122	43.3	5249
Blekinge	Sölvesborg	Sölvesborg STP	Water	Influent		061127-28	-	5260
Blekinge	Sölvesborg	Sölvesborg STP	Water	Effluent		061127-28	-	5261

County	City	Site	Matrix	Information	Coordinates	Sample date	DW. %	Sample ID
Blekinge	Sölvesborg	Sölvesborg STP	Sludge			061128	36.2	5263
Blekinge	Karlskrona	Karlskrona hospital	Water	Effluent		061205	-	5279
Blekinge	Karlshamn	Karlshamns hospital	Water	Effluent			-	5482
Dalarna	Mora	Solvikens STP	Water	Effluent		060925-28	-	5010
Dalarna	Falun	Främby STP	Water	Effluent		v39 2006	-	5013
Dalarna	Ludvika	Gårlängens STP	Water	Effluent		060925-29	-	5036
Dalarna	Säter	Säters STP	Water	Effluent		v40 mån-fre 2006		5040
Dalarna	Avesta	Krylbo STP	Water	Effluent		060925.26.29	-	5058
Dalarna	Avesta	Krylbo STP	Sludge			060925-27		5060
Dalarna	Borlänge	Fågelmåra landfill	Water	Leachate water		060925-29	-	5069
Dalarna	Borlänge	Fagersta By STP	Water	Effluent		060925-28	-	5070
Dalarna	Borlänge	Fagersta By STP	Sludge			060925-29	47.3	5071
Gotland	Gothem	Gothemsån Hörsne	Water	Surface water	X6384913; Y1667216	061019	-	5108
Gotland	Visby	Visby STP	Water	Effluent	X6391515; Y1647282	061019	-	5109
Norrbottn	Luleå	Uddebo STP	Water	Effluent		061007-16	-	5080
Norrbottn	Luleå	Uddebo STP	Sludge			061007-16	35.1	5082
Norrbottn	Piteå	Sandholmens STP	Water	Effluent		060926-061002		5084
Norrbottn	Gällivare	Kavahedens STP	Water	Effluent		v41 2006	-	5087
Södermanland	Strängnäs	Mariefreds STP	Water	Influent		060911	-	4970
Södermanland	Strängnäs	Mariefreds STP	Water	Effluent		060911	-	4971
Södermanland	Strängnäs	Mariefreds STP	Sludge			060911	40.5	4973
Södermanland	Strängnäs	Strängnäs STP	Water	Influent		060912	-	4974
Södermanland	Strängnäs	Strängnäs STP	Water	Effluent		060912	-	4975
Södermanland	Strängnäs	Strängnäs STP	Sludge			060912	44.2	4976
Södermanland	Flen	Flen STP	Water	Influent		060907-13	-	4996
Södermanland	Flen	Flen STP	Water	Effluent		060907-13	-	4997
Södermanland	Flen	Flen STP	Sludge			060913	40.5	4999
Södermanland	Katrineholm	Rosenholm	Water	Influent		060926	-	5026
Södermanland	Katrineholm	Rosenholm	Water	Effluent		060926	-	5027



County	City	Site	Matrix	Information	Coordinates	Sample date	DW. %	Sample ID
Södermanland	Katrineholm	Rosenholm	Sludge			060926	49.0	5029
Södermanland	Trosa	Trosa STP	Water	Influent		060926	-	5048
Södermanland	Trosa	Trosa STP	Water	Effluent		060926	-	5049
Södermanland	Trosa	Trosa STP	Water	Water, wetland		060926	-	5050
Södermanland	Trosa	Trosa STP	Sludge			060926	43.8	5052
Södermanland	Eskilstuna	Ekeby STP	Sludge			061107		5131
Södermanland	Eskilstuna	Ekeby STP	Water	Influent		061107	-	5133
Södermanland	Eskilstuna	Ekeby STP	Water	Effluent		061107	-	5134
Södermanland	Eskilstuna	Ekeby STP	Water	wetland		061107	-	5135
Värmland	Säffle	Säffle STP	Sludge			060925	27	5011
Värmland	Karlstad	Sjöstad STP	Water	Influent	6587178.228; 1371426.998	060911-18	-	4985
Värmland	Karlstad	Sjöstad STP	Water	Effluent	6587178.228; 1371426.998	060911-18	-	4987
Värmland	Karlstad	Sjöstad STP	Sludge		6587178.228; 1371426.998	060918	33.8	4989
Värmland	Kristinehamn	Fiskartorpet STP	Water	Influent	6578124; 1401080	060920	-	4991
Värmland	Kristinehamn	Fiskartorpet STP	Water	Effluent	6578124; 1401080	060920	-	4992
Värmland	Kristinehamn	Fiskartorpet STP	Sludge		6578124; 1401080	060919	25.8	4994
Värmland	Arvika	Vik STP	Sludge			061002	16.2	5019
Västerbotten	Lycksele	Lycksele STP	Sludge			061002	42.5	5038
Västerbotten	Skellefteå	Tuvans STP	Sludge			061002	32.2	5039

**Appendix 3. Results: Pharmaceuticals and metabolites (1st group) in water, ng/l.**

County/Type	City	Site	Information	Sample ID	Propofol	Fentanyl	Dextropropoxyhene	Bromocriptine	Thioridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitrazepam
background		Tärnan	Surface water	5563	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
background		Gårdsjön	Surface water	5642	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
background		Härsevattnet	Surface water	5643	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Karlshamn WTP	Drinking water	5056	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Karlshamn WTP (Mieån)	Surface water Incoming	5054	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Lyckeby VV	Drinking water	5047	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Lyckeby WTP (Lyckebyån)	Surface water incoming	5046	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Ronneby	Kärragårdens WTP	Drinking water	4979	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Ronneby	Kärragårdens WTP (Listerån)	Surface water Incoming	4978	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Stora Essingen	Surface water	5290	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Årstaviken	Surface water	5291	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Riddarfjärden	Surface water	5293	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	outside Bromma STP	Surface water	5294	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	outside Henriksdals STP	Surface water	5295	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Vasa museum	Surface water	5501	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Gotland	Gothem	Gothemsån Hörsne	Surface water	5108	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Sternö STP	Effluent	5022	200	<2	<2	<2	<2	<3	3	<1	<1	37	<1
Blekinge	Karlshamn	Mörrums STP	Effluent	5032	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	34	<1
Blekinge	Karlshamn	Karlshamns sjukhus	Effluent	5482	98	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Koholmen STP	Effluent	5043	5.7	<2	<2	<2	<2	<3	<1	<1	<1	53	<1
Blekinge	Karlskrona	Karlskrona sjukhus	Effluent	5279	7.4	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Olofström	Jämshögs STP	Effluent	5247	2.8	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Ronneby	Rustorps STP	Effluent	4982	2.3	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Sölvesborg	Sölvesborg STP	Effluent	5261	7.1	<2	<2	<2	<2	<3	<1	<1	<1	23	<1
Dalarna	Avesta	Krylbo STP	Effluent	5058	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	36	<1

County/Type	City	Site	Information	Sample ID	Propofol	Fentanyl	Dextropropoxyhene	Bromocriptine	Thioridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitrazepam
Dalarna	Borlänge	Fagersta By STP	Effluent	5070	<0.6	<2	<2	<2	<2	<3	7.8	<1	<1	<1	<1
Dalarna	Falun	Främby STP	Effluent	5013	18	<2	<2	<2	<2	<3	<1	5	<1	41	<1
Dalarna	Ludvika	Gärilångens STP	Effluent	5036	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	32	<1
Dalarna	Mora	Solvikens STP	Effluent	5010	0.8	<2	<2	<2	<2	<3	<1	10	<1	<1	<1
Dalarna	Säter	Sätters STP	Effluent	5040	12	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Henriksdal.Sickla	Effluent	5074	29	<2	<2	<2	<2	<3	<1	9.3	<1	<1	<1
diffuse	Stockholm	Bromma	Effluent	5072	<0.6	<2	<2	<2	<2	<3	8	<1	<1	<1	<1
diffuse	Stockholm	Hammarby Sjöstad	Effluent	5076	140	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Effluent w. 1-2	5510	19	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Effluent w. 3-5	5512	29	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Effluent w. 5-6	5514	510	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Gotland	Visby	Visby STP	Effluent	5109	10	<2	<2	<2	<2	<3	<1	14	<1	<1	<1
Norrbottn	Gällivare	Kavahedens STP	Effluent	5087	14	<2	<2	<2	<2	<3	<1	<1	<1	30	<1
Norrbottn	Luleå	Uddebo STP	Effluent	5080	<3	<2	<2	<2	<2	<3	<1	12	<1	<1	<1
Norrbottn	Piteå	Sandholmens STP	Effluent	5084	0.9	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Eskilstuna	Ekeby STP	Effluent	5134	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	29	<1
Södermanland	Eskilstuna	Ekeby STP,	Effluent, wetland	5135	1.0	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Flen	Flen STP	Effluent	4997	1.7	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Katrineholm	Rosenholm	Effluent	5027	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Strängnäs	Mariefreds STP	Effluent	4971	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Strängnäs	Strängnäs STP	Effluent	4975	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Trosa	Trosa STP	Effluent	5049	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Trosa	Trosa STP	Effluent wetland	5050	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Värmland	Karlstad	Sjöstad STP	Effluent	4987	14	<2	<2	<2	<2	<3	<1	5	<1	<1	<1
Värmland	Kristinehamn	Fiskartorpet STP	Effluent	4992	0.9	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Sternö STP	Influent	5021	16	<2	<2	<2	<2	<3	<1	31	<1	<1	<1
Blekinge	Karlshamn	Mörrums STP	Influent	5031	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Koholmen STP	Influent	5042	29	<2	<2	<2	<2	<3	<1	17	<1	66	<1
Blekinge	Olofström	Jämshögs STP	Influent	5246	5.4	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1

County/Type	City	Site	Information	Sample ID	Propofol	Fentanyl	Dextropropoxyhene	Bromocriptine	Thioridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitrazepam
Blekinge	Ronneby	Rustorps RV	Influent	4981	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Sölvesborg	Sölvesborg STP	Influent	5260	1.7	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Karlskoga	Aggerud STP	Influent	5066	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Karlstad	Sjöstad STP	Influent	4986	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Lindesberg	Lindesberg STP	Influent	5121	1.2	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Influent w. 1-2	5509	21	<2	<2	<2	<2	<3	20	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Influent w. 3-4	5511	15	<2	<2	<2	<2	<3	20	<1	<1	<1	<1
diffuse	Stockholm	Käppala	Influent w. 5-6	5513	17	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Eskilstuna	Ekeby STP	Influent	5133	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Flen	Flen STP	Influent	4996	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Katrineholm	Rosenholm	Influent	5026	<0.6	<2	<2	<2	<2	<3	17	<1	<1	<1	<1
Södermanland	Strängnäs	Mariefreds STP	Influent	4970	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	63	<1
Södermanland	Strängnäs	Strängnäs STP	Influent	4974	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Södermanland	Trosa	Trosa STP	Influent	5048	<0.6	<2	<2	<2	<2	<3	13	<1	<1	<1	<1
Värmland	Karlstad	Sjöstad STP	Influent	4985	8.3	<2	<2	<2	<2	<3	<1	19	<1	<1	<1
Värmland	Kristinehamn	Fiskartorpet STP	Influent	4991	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Bubbetorp deponi	Leachate water	5041	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
Dalarna	Borlänge	Fågemyra deponi	Leachate water	5069	<0.6	<2	<2	<2	<2	<3	260	<1	<1	<1	<1
point source	Borlänge	Fågemyra landfill	Leachate water	5538	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
point source	Bro	Högbytorp landfill	Leachate water	5475	18	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1
point source	Kristinehamn	Strandmossen landfill	Leachate water	5481	<0.6	<2	<2	<2	<2	<3	<1	<1	<1	<1	<1

**Appendix 4. Results: Pharmaceuticals and metabolites (2nd group) in water, ng/l.**

County	City	Site	Information	Sample ID	Diaze pam	Oxaze pam	Parox etine	Citalo pram	Zopi clone	Caff eine	Norpro poxy phene	Nor fenta nyl	Zopiclo ne N-oxide	N-demethyl flunitr azepam	7-amino flunitr azepam	Nordiaze pam
background		Tärnan	Surface water	5563	<0.8	<4	<1	<0.3	<1	27	<5	<5	<5	<5	<5	<3
background		Gårdsjön	Surface water	5642	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
background		Härsevattnet	Surface water	5643	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Karlshamn	Karlshamns WTP	Drinking water	5056	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Karlshamn	Karlshamns WTP (Mieån)	Surface water Incoming	5054	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Karlskrona	Lyckeby VV	Drinking water	5047	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Karlskrona	Lyckeby WTP (Lyckebyån)	Surface water incoming	5046	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Ronneby	Kärragårdens WTP	Drinking water	4979	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Blekinge	Ronneby	Kärragårdens WTP (Listerån)	Surface water Incoming	4978	<0.8	5	<1	<0.3	<1	15	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Stora Essingen	Surface water	5290	<0.8	<4	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Årstaviken	Surface water	5291	<0.8	15	<1	<0.3	<1	250	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Riddarfjärden	Surface water	5293	<0.8	12	<1	<0.3	<1	140	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	outside Bromma STP	Surface water	5294	<0.8	15	<1	<0.3	<1	180	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	outside Henriksdals STP	Surface water	5295	<0.8	21	<1	<0.3	<1	120	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Vasa museum	Surface water	5501	<0.8	9	<1	<0.3	<1	180	<5	<5	<5	<5	<5	<3
Gotland	Gothem	Gothemsån Hörsne	Surface water	5108	<0.8	24	<1	<0.3	<1	170	<5	<5	<5	<5	<5	<3
Blekinge	Karlshamn	Sternö STP	Effluent	5022	<0.8	1200	27	110	<1	<8	<5	<5	<5	<5	<5	15
Blekinge	Karlshamn	Mörrums STP	Effluent	5032	<0.8	700	37	120	<1	680	<5	<5	<5	<5	<5	9.1
Blekinge	Karlshamn	Karlshamns sjukhus	Effluent	5482	<0.8	79	<1	49	<1	110000	<5	<5	<5	<5	<5	<3
Blekinge	Karlskrona	Koholmen STP	Effluent	5043	<0.8	890	<1	100	<1	300	<5	<5	<5	<5	<5	<3
Blekinge	Karlskrona	Karlskrona sjukhus	Effluent	5279	<0.8	240	<1	<0.3	<1	150000	<5	<5	<5	<5	<5	<3
Blekinge	Olofström	Jämshögs STP	Effluent	5247	<0.8	320	<1	51	<1	12000	<5	<5	<5	<5	<5	<3
Blekinge	Ronneby	Rustorps STP	Effluent	4982	<0.8	530	<1	95	<1	260	<5	<5	<5	<5	<5	<3
Blekinge	Sölvesborg	Sölvesborg STP	Effluent	5261	<0.8	660	<1	85	<1	480	<5	<5	<5	<5	26	<3
Dalarna	Avesta	Krylbo STP	Effluent	5058	<0.8	810	20	65	<1	390	<5	<5	<5	<5	<5	29

County	City	Site	Information	Sample ID	Diazepam	Oxazepam	Paroxetine	Citalopram	Zopiclone	Caffeine	Norpropoxyphene	Norfentanyl	Zopiclone N-oxide	N-demethylflunitrazepam	7-amino flunitrazepam	Nordiazepam
Dalarna	Borlänge	Fagersta By STP	Effluent	5070	<0.8	730	<1	67	<1	2100	<5	<5	89	<5	<5	23
Dalarna	Falun	Främby STP	Effluent	5013	<0.8	470	<1	78	<1	230	<5	<5	<5	<5	<5	<3
Dalarna	Ludvika	Gärilångens STP	Effluent	5036	<0.8	850	<1	110	<1	800	<5	<5	<5	<5	<5	20
Dalarna	Mora	Solvikens STP	Effluent	5010	<0.8	600	<1	71	<1	230	<5	<5	<5	<5	<5	<3
Dalarna	Säter	Sätters STP	Effluent	5040	<0.8	700	<1	110	<1	<8	<5	<5	<5	<5	<5	28
diffuse	Stockholm	Henriksdal.Sickla	Effluent	5074	<0.8	620	<1	85	<1	<8	<5	<5	<5	<5	<5	19
diffuse	Stockholm	Bromma	Effluent	5072	<0.8	460	17	21	<1	7500	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Hammarby Sjöstad	Effluent	5076	<0.8	570	24	98	<1	220	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Käppala	Effluent w. 1-2	5510	<0.8	220	<1	67	<1	<8	<5	<5	<5	<5	<5	4.7
diffuse	Stockholm	Käppala	Effluent w. 3-5	5512	<0.8	200	<1	58	<1	150	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Käppala	Effluent w. 5-6	5514	<0.8	290	<1	59	<1	<8	<5	<5	<5	<5	<5	<3
Gotland	Visby	Visby STP	Effluent	5109	<0.8	580	56	57	<1	960	<5	<5	<5	<5	<5	14
Norrbottn	Gällivare	Kavahedens STP	Effluent	5087	<0.8	270	<1	47	<1	16000	<5	<5	<5	<5	<5	<3
Norrbottn	Luleå	Uddebo STP	Effluent	5080	<0.8	310	26	39	<1	4800	<5	<5	<5	<5	<5	<3
Norrbottn	Piteå	Sandholmens STP	Effluent	5084	<0.8	480	<1	91	<1	43000	<5	<5	<5	<5	<5	17
Södermanland	Eskilstuna	Ekeby STP	Effluent	5134	<0.8	360	33	83	<1	92	<5	<5	<5	<5	<5	<3
Södermanland	Eskilstuna	Ekeby STP,	Effluent, wetland	5135	<0.8	380	21	36	<1	400	<5	<5	<5	<5	<5	17
Södermanland	Flen	Flen STP	Effluent	4997	<0.8	470	<1	84	<1	<8	<5	<5	<5	<5	<5	<3
Södermanland	Katrineholm	Rosenholm	Effluent	5027	<0.8	750	22	86	<1	6300	<5	<5	<5	<5	<5	26
Södermanland	Strängnäs	Mariefreds STP	Effluent	4971	<0.8	370	34	72	<1	11000	<5	<5	<5	<5	<5	<3
Södermanland	Strängnäs	Strängnäs STP	Effluent	4975	<0.8	440	28	89	<1	760	<5	<5	<5	<5	<5	<3
Södermanland	Trosa	Trosa STP	Effluent	5049	<0.8	600	23	85	<1	14000	<5	<5	<5	<5	<5	<3
Södermanland	Trosa	Trosa STP	Effluent wetland	5050	<0.8	330	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	11
Värmland	Karlstad	Sjöstad STP	Effluent	4987	<0.8	800	<1	110	<1	380	<5	<5	<5	<5	<5	30
Värmland	Kristinehamn	Fiskartorpet STP	Effluent	4992	<0.8	980	<1	110	<1	1400	<5	<5	<5	<5	<5	<3
Blekinge	Karlshamn	Sternö STP	Influent	5021	<0.8	1200	<1	100	<1	110000	<5	<5	<5	<5	<5	<3
Blekinge	Karlshamn	Mörrums STP	Influent	5031	<0.8	680	<1	180	<1	110000	<5	<5	230	<5	<5	<3
Blekinge	Karlskrona	Koholmen STP	Influent	5042	<0.8	1100	<1	62	<1	54000	<5	<5	<5	<5	<5	<3
Blekinge	Olofström	Jämshögs STP	Influent	5246	<0.8	320	41	49	<1	36000	<5	<5	<5	<5	<5	<3

County	City	Site	Information	Sample ID	Diaze pam	Oxaze pam	Parox etine	Citalo pram	Zopi clone	Caff eine	Norpro poxy phene	Nor fenta nyl	Zopiclo ne N-oxide	N-demethyl flunitr azepam	7-amino flunitr azepam	Nordiaze pam
Blekinge	Ronneby	Rustorps RV	Influent	4981	<0.8	540	<1	95	<1	88000	<5	<5	<5	<5	<5	<3
Blekinge	Sölvesborg	Sölvesborg STP	Influent	5260	<0.8	610	45	64	<1	39000	<5	<5	<5	<5	78	<3
diffuse	Karlskoga	Aggerud STP	Influent	5066	<0.8	120	<1	13	<1	15000	<5	<5	<5	<5	<5	<3
diffuse	Karlstad	Sjöstad STP	Influent	4986	<0.8	170	<1	27	<1	17000	<5	<5	<5	<5	<5	25
diffuse	Lindesberg	Lindesberg STP	Influent	5121	<0.8	33	<1	12	<1	13000	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Käppala	Influent w. 1-2	5509	<0.8	250	70	80	<1	50000	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Käppala	Influent w. 3-4	5511	<0.8	210	<1	77	<1	110000	<5	<5	<5	<5	<5	<3
diffuse	Stockholm	Käppala	Influent w. 5-6	5513	<0.8	390	<1	71	<1	96000	<5	<5	<5	<5	*	<3
Södermanland	Eskilstuna	Ekeby STP	Influent	5133	<0.8	450	<1	95	<1	58000	<5	<5	<5	<5	<5	<3
Södermanland	Flen	Flen STP	Influent	4996	<0.8	450	<1	38	<1	99000	<5	<5	<5	<5	<5	<3
Södermanland	Katrineholm	Rosenholm	Influent	5026	<0.8	920	24	120	<1	150000	<5	<5	<5	<5	<5	<3
Södermanland	Strängnäs	Mariefreds STP	Influent	4970	<0.8	360	<1	50	<1	88000	<5	<5	<5	<5	<5	<3
Södermanland	Strängnäs	Strängnäs STP	Influent	4974	<0.8	400	<1	68	<1	45000	<5	<5	<5	<5	<5	<3
Södermanland	Trosa	Trosa STP	Influent	5048	<0.8	600	<1	57	<1	98000	<5	<5	<5	<5	<5	<3
Värmland	Karlstad	Sjöstad STP	Influent	4985	<0.8	760	<1	110	<1	96000	<5	<5	<5	<5	<5	27
Värmland	Kristinehamn	Fiskartorpet STP	Influent	4991	<0.8	810	68	51	<1	55000	<5	<5	<5	<5	<5	28
Blekinge	Karlskrona	Bubbetorp deponi	Leachate water	5041	<0.8	110	<1	<0.3	<1	<8	<5	<5	<5	<5	<5	<3
Dalarna	Borlänge	Fågemyra deponi	Leachate water	5069	<0.8	12	<1	26	<1	550000	<5	<5	<5	<5	<5	<3
point source	Borlänge	Fågemyra landfill	Leachate water	5538	<0.8	24	<1	<0.3	<1	824	<5	<5	<5	<5	<5	<3
point source	Bro	Högbytorp landfill	Leachate water	5475	<0.8	24	1200	<0.3	<1	370000	<5	<5	<5	<5	1030	<3
point source	Kristinehamn	Strandmossen landfill	Leachate water	5481	<0.8	9.6	<1	<0.3	<1	590	<5	<5	<5	<5	<5	<3

\* No data on 7-aminoflunitrazepam in the influent water sample from Stockholm (Sample ID 5513) due to interferences in the chromatography.

**Appendix 5. Results: Pharmaceuticals and metabolites (1st group) in sludge (ng/g dw), sediment (ng/g dw) and fish (ng/g ww).**

County	City	Site	Matrix	Sample ID	Propofol	Fentanyl	Dextropropoxyphen	Bromocriptine	Thioridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitrazepam
Background		Krageholmssjön	Fish	5243	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
Background		Lilla Öresjön	Fish	5244	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
Background		Övre Skårsjön	Fish	5245	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
Background		Övre Skårsjön	Sediment	5240	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
Background		Lilla Öresjön	Sediment	5241	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	3.3
Background		Krageholmssjön	Sediment	5242	<0.1	<0.1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Riddarfjärden	Fish	5526	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Stora Essingen	Fish	5527	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Årstaviken	Fish	5528	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Henriksdahls STP	Fish	5529	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Bromma STP	Fish	5530	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Vasamuseum	Fish	5531	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Stora Essingen	Sediment	5287	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.6	0.9
National-diffuse	Stockholm	Årstaviken	Sediment	5288	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Riddarfjärden	Sediment	5296	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	outside Bromma STP	Sediment	5297	4.4	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	0.6
National-diffuse	Stockholm	outside Henriksdals STP	Sediment	5298	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	<0.3	<0.5	<0.5
National-diffuse	Stockholm	Vasa museum	Sediment	5502	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	1.6	<0.5	<0.5
Blekinge	Karlshamn	Sternö STP	Sludge	5024	0.4	<1	<0.9	<1	<1	101	<0.5	0.2	38	<0.5	<0.5
Blekinge	Karlshamn	Mörrums STP	Sludge	5034	0.2	<1	<0.9	<1	<1	<0.8	<0.5	2.2	11	<0.5	<0.5
Blekinge	Karlskrona	Koholmen STP	Sludge	5044	<0.1	<1	<0.9	<1	<1	9.8	<0.5	0.6	100	<0.5	<0.5
Blekinge	Olofström	Jämshögs STP	Sludge	5249	<0.1	<1	<0.9	<1	<1	6.2	<0.5	<0.2	11	<0.5	<0.5
Blekinge	Ronneby	Rustorps RV	Sludge	4983	<0.1	<1	<0.9	<1	<1	11.5	<0.5	<0.2	200	<0.5	<0.5
Blekinge	Sölvesborg	Sölvesborg STP	Sludge	5263	<0.1	<1	<0.9	<1	<1	17	<0.5	0.5	170	<0.5	<0.5
Dalarna	Avesta	Krylbo STP	Sludge	5060	<0.1	<1	<0.9	<1	<1	68	<0.5	<0.2	61	<0.5	<0.5
Dalarna	Borlänge	Fagersta By STP	Sludge	5071	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	79	<0.5	<0.5
National diffuse	Alingsås	Nolhaga STP	Sludge	5223	0.4	<1	<0.9	<1	<1	18	<0.5	<0.2	51	<0.5	<0.5
National diffuse	Bollebygd	Bollebygd STP	Sludge	5225	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	89	<0.5	<0.5



County	City	Site	Matrix	Sample ID	Propofol	Fentanyl	Dextropropoxyphen	Bromocriptine	Thioridazine	Clozapine	Risperidone	Zolpidem	Sertraline	Fluoxetine	Flunitrazepam
National diffuse	Borås	Gässlösa STP	Sludge	5227	0.7	<1	<0.9	<1	<1	16	<0.5	<0.2	38	<0.5	<0.5
National diffuse	Eslöv	Ellinge STP	Sludge	5226	<0.1	<1	<0.9	<1	<1	12	<0.5	<0.2	24	<0.5	<0.5
National diffuse	Floda	Floda STP	Sludge	5222	0.2	<1	<0.9	<1	<1	13	<0.5	<0.2	35	<0.5	<0.5
National diffuse	Göteborg	Ryaverket STP	Sludge	5221	0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	57	<0.5	<0.5
National diffuse	Stockholm	Bromma	Sludge	5073	0.1	<1	<0.9	<1	<1	<0.8	<0.5	1.4	84	<0.5	<0.5
National diffuse	Stockholm	Henriksdal, Sickla	Sludge	5075	0.3	<1	<0.9	<1	<1	35	<0.5	3.8	87	<0.5	<0.5
National diffuse	Stockholm	Hammarby Sjöstad SL1	Sludge	5078	<0.1	<1	1	<1	<1	6	<0.5	1	18	<0.5	<0.5
National diffuse	Stockholm	Käppala STP	Sludge	5505	1.2	<1	<0.9	<1	<1	13	<0.5	1.8	40	<0.5	<0.5
National diffuse	Stockholm	Käppala STP	Sludge	5506	4.5	<1	<0.9	<1	<1	13	<0.5	3	36	<0.5	<0.5
National diffuse	Stockholm	Käppala STP	Sludge	5507	1.1	<1	<0.9	<1	<1	18	<0.5	2.5	54	<0.5	<0.5
National diffuse	Stockholm	Käppala STP	Sludge	5508	3.2	<1	<0.9	<1	<1	8.5	<0.5	2	26	<0.5	<0.5
National diffuse	Umeå	Umeå STP	Sludge	5220	2.0	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	61	<0.5	<0.5
Norrbottn	Luleå	Uddebo STP	Sludge	5082	<1	<1	<0.9	<1	<1	52	<0.5	1.4	81	<0.5	<0.5
Södermanland	Eskilstuna	Ekeby STP	Sludge	5131	0.2	<1	<0.9	<1	<1	45	<0.5	3.2	35	<0.5	<0.5
Södermanland	Flen	Flen STP	Sludge	4999	<0.1	<1	<0.9	<1	<1	35	<0.5	1	58	<0.5	<0.5
Södermanland	Katrineholm	Rosenholm	Sludge	5029	0.2	<1	<0.9	<1	<1	54	<0.5	2	8	<0.5	<0.5
Södermanland	Strängnäs	Mariefreds STP	Sludge	4973	<0.1	<1	<0.9	<1	<1	3.8	<0.5	0.7	22	<0.5	<0.5
Södermanland	Strängnäs	Strängnäs STP	Sludge	4976	<0.1	<1	<0.9	<1	<1	54	<0.5	1	98	<0.5	<0.5
Södermanland	Trosa	Trosa STP	Sludge	5052	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	37	<0.5	<0.5
Värmland	Arvika	Vik STP	Sludge	5019	0.3	<1	<0.9	<1	<1	10.6	<0.5	1.2	46	<0.5	<0.5
Värmland	Karlstad	Sjöstad STP	Sludge	4989	<0.1	<1	<0.9	<1	<1	23.6	<0.5	<0.2	85	<0.5	<0.5
Värmland	Kristinehamn	Fiskartorpet STP	Sludge	4994	<0.1	<1	<0.9	<1	<1	49.6	<0.5	1.7	210	<0.5	<0.5
Värmland	Säffle	Säffle STP	Sludge	5011	<0.1	<1	<0.9	<1	<1	<0.8	<0.5	<0.2	140	<0.5	<0.5
Västerbotten	Lycksele	Lycksele STP	Sludge	5038	<0.1	<1	<0.9	<1	<1	15	<0.5	<0.2	140	<0.5	<0.5
Västerbotten	Skellefteå	Tuvans STP	Sludge	5039	<0.1	<1	<0.9	<1	<1	38	<0.5	2	300	<0.5	<0.5

**Appendix 6. Results: Pharmaceuticals and metabolites (2nd group) in sludge (ng/g dw), sediment (ng/g dw) and fish (ng/g ww).**

County	City	Site	Matrix	Sample ID	Diazepam	Oxazepam	Paroxetine	Citalopram	Zopiclone	Caffeine	Norfentanyl	Norpropoxyphene	Zopiclone N-oxide	N-demethylflunitrazepam	7-amino flunitrazepam	Nordiazepam
Background		Krageholmssjön	Fish	5243	<0.5	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1
Background		Lilla Öresjön	Fish	5244	<0.5	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1
Background		Övre Skärsjön	Fish	5245	<0.5	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1
Background		Övre Skärsjön	Sediment	5240	<0.5	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1
Background		Lilla Öresjön	Sediment	5241	<0.5	<0.5	<1	<0.5	<0.5	<1	110	<1	<1	<1	<1	<1
Background		Krageholmssjön	Sediment	5242	<0.5	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Riddarfjärden	Fish	5526	<0.5	<1	<0.5	<=0.3	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Stora Essingen	Fish	5527	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Årstaviken	Fish	5528	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Henriksdahls STP	Fish	5529	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Bromma STP	Fish	5530	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Vasamuseum	Fish	5531	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Stora Essingen	Sediment	5287	<0.5	<1	<0.5	0.8	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Årstaviken	Sediment	5288	<0.5	<1	<0.5	1.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Riddarfjärden	Sediment	5296	<0.5	<1	<0.5	<0.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	outside Bromma STP	Sediment	5297	<0.5	<1	<0.5	1.5	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	outside Henriksdals STP	Sediment	5298	<0.5	<1	<0.5	1.8	<1	<2	<1	<1	<1	<1	<1	<1
National-diffuse	Stockholm	Vasa museum	Sediment	5502	<0.5	<1	<0.5	1.4	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Sternö STP	Sludge	5024	<0.5	30	<0.5	98	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Karlshamn	Mörrums STP	Sludge	5034	<0.5	<1	<0.5	96	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Karlskrona	Koholmen STP	Sludge	5044	<0.5	99	<0.5	100	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Olofström	Jämshögs STP	Sludge	5249	<0.5	29	<0.5	45	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Ronneby	Rustorps RV	Sludge	4983	<0.5	53	<0.5	140	<1	<2	<1	<1	<1	<1	<1	<1
Blekinge	Sölvesborg	Sölvesborg STP	Sludge	5263	<0.5	110	<0.5	150	<1	<2	<1	<1	<1	<1	<1	<1
Dalarna	Avesta	Krylbo STP	Sludge	5060	<0.5	<1	<0.5	210	<1	<2	<1	<1	<1	<1	<1	<1
Dalarna	Borlänge	Fagersta By STP	Sludge	5071	<0.5	40	<0.5	74	<1	<2	<1	<1	<1	<1	<1	<1

County	City	Site	Matrix	Sample ID	Diazepam	Oxazepam	Paroxetine	Citalopram	Zopiclone	Caffeine	Norfentanyl	Norpropoxyphene	Zopiclone N-oxide	N-demethylflunitrazepam	7-amino flunitrazepam	Nordiazepam
National diffuse	Alingsås	Nolhaga STP	Sludge	5223	<0.5	25	<0.5	82	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Bollebygd	Bollebygd STP	Sludge	5225	<0.5	72	<0.5	77	<1	130	<1	<1	<1	<1	<1	<1
National diffuse	Borås	Gässlösa STP	Sludge	5227	<0.5	<1	<0.5	110	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Eslöv	Ellinge STP	Sludge	5226	<0.5	<1	<0.5	57	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Floda	Floda STP	Sludge	5222	<0.5	27	<0.5	78	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Göteborg	Ryaverket STP	Sludge	5221	<0.5	<1	<0.5	110	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Bromma	Sludge	5073	<0.5	<1	<0.5	110	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Henriksdal, Slickla	Sludge	5075	<0.5	<1	<0.5	150	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Hammarby Sjöstad SL1	Sludge	5078	<0.5	<1	<0.5	23	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Käppala STP	Sludge	5505	<0.5	<1	<0.5	110	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Käppala STP	Sludge	5506	<0.5	<1	<0.5	130	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Käppala STP	Sludge	5507	<0.5	<1	<0.5	120	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Stockholm	Käppala STP	Sludge	5508	<0.5	<1	<0.5	72	<1	<2	<1	<1	<1	<1	<1	<1
National diffuse	Umeå	Umeå STP	Sludge	5220	<0.5	<1	<0.5	110	<1	<2	<1	<1	<1	<1	<1	<1
Norrbottnen	Luleå	Uddebo STP	Sludge	5082	<0.5	<1	<0.5	95	<1	<2	<1	<1	<1	<1	<1	<1
Södermanland	Eskilstuna	Ekeby STP	Sludge	5131	<0.5	<1	<0.5	150	<1	<2	<1	<1	<1	<1	<1	<1
Södermanland	Flen	Flen STP	Sludge	4999	<0.5	14	<0.5	97	<1	<2	<1	<1	<1	<1	<1	<1
Södermanland	Katrineholm	Rosenholm	Sludge	5029	<0.5	<1	<0.5	61	<1	<2	<1	<1	<1	<1	<1	<1
Södermanland	Strängnäs	Mariefreds STP	Sludge	4973	<0.5	<1	<0.5	62	<1	<2	<1	<1	<1	<1	<1	<1
Södermanland	Strängnäs	Strängnäs STP	Sludge	4976	<0.5	<1	<0.5	150	<1	170	<1	<1	<1	<1	<1	<1
Södermanland	Trosa	Trosa STP	Sludge	5052	<0.5	45	<0.5	48	<1	78	<1	<1	<1	<1	<1	<1
Värmland	Arvika	Vik STP	Sludge	5019	<0.5	34	<0.5	66	<1	<2	<1	<1	<1	<1	<1	<1
Värmland	Karlstad	Sjöstad STP	Sludge	4989	<0.5	<1	<0.5	99	<1	<2	<1	<1	<1	<1	<1	<1
Värmland	Kristinehamn	Fiskartorpet STP	Sludge	4994	<0.5	71	<0.5	140	<1	<2	<1	<1	<1	<1	<1	<1
Värmland	Säffle	Säffle STP	Sludge	5011	<0.5	<1	<0.5	130	<1	71	<1	<1	<1	<1	<1	<1
Västerbotten	Lycksele	Lycksele STP	Sludge	5038	<0.5	17	<0.5	70	<1	560	<1	<1	<1	<1	<1	<1
Västerbotten	Skelefteå	Tuvans STP	Sludge	5039	<0.5	<1	<0.5	120	<1	<2	<1	<1	<1	<1	<1	<1