Statens forurensningstilsyn
Norwegian Pollution Control Authority

Current State of Knowledge and Monitoring Requirements

HUMAN AND VETERINARY PHARMACEUTICALS, NARCOTICS, AND PERSONAL CARE PRODUCTS IN THE ENVIRONMENT

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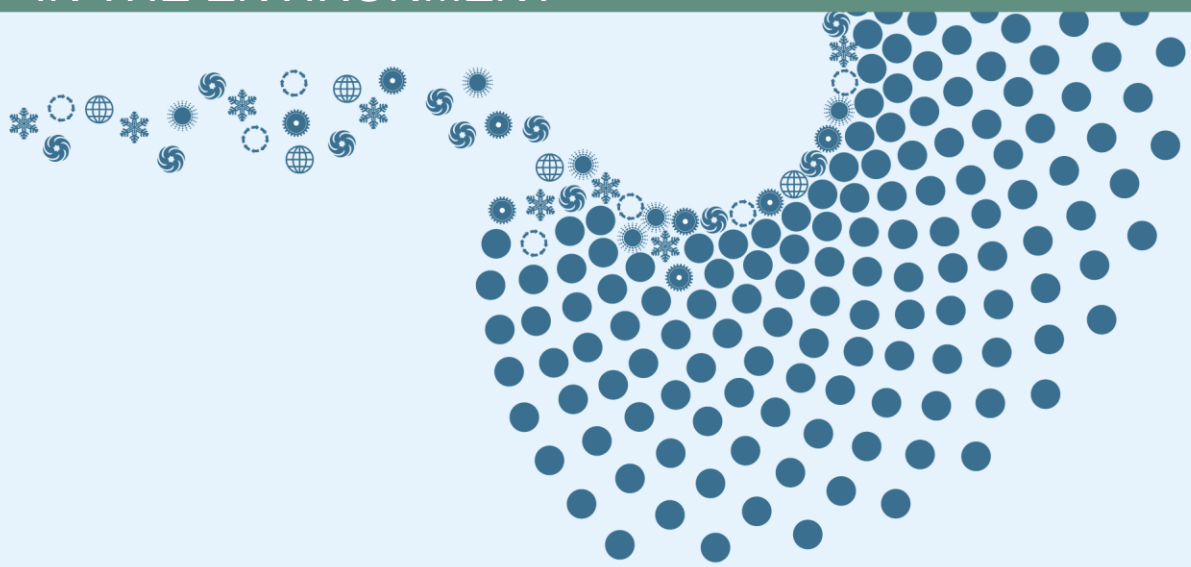

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Human and Veterinary Pharmaceuticals, Narcotics, and Personal Care Products in the Environment

Report
2325/2007

Current State of Knowledge and Monitoring Requirements

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Preface

Many tonnes of human and veterinary pharmaceuticals are sold in Norway every year, whilst it is estimated that many kilos of narcotics are illegally used. The personal care products market in Norway is worth several billion NOK a year. As with many other compounds their eventual sink is the sea or great lakes. The ecotoxicological risk these substances pose to the environment is less clear. Due to their specific mechanisms of biologically activity these substances may exert chronic long-term risks especially to the aquatic environment.

This report addresses the need to better understand the issues associated with human and veterinary pharmaceuticals, narcotics, and personal care products in the environment through performing a review and assessment of existing data and current and planned activities.

On behave of the Norwegian Control Pollution Authority (SFT) the three environmental research institutes IVL (Sweden), NILU (Norway), and NIVA (Norway) have performed a review of the current state of the knowledge on PPCPs and selected compounds prioritised for further monitoring.

SFT, Oslo, January 2008

Anne Mari Opheim
Deputy Director for the Department of Chemicals and Local Environmental Management

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1. Summary

Many tonnes of human and veterinary pharmaceuticals (HPs and VPs) are sold in Norway every year, whilst it is estimated that many kilos of narcotics are illegally used. The personal care products (PCPs) market in Norway is worth several billion NOK a year. These xenobiotic compounds (human and veterinary pharmaceuticals, narcotics, and personal care products) are often combined under the common heading: Pharmaceuticals and Personal Care Products (PPCPs). In contrast to the common use this report also include narcotics into this term.

PPCPs and their metabolites predominantly end up in rivers, streams and fjords via the sewage network that focuses the excreted compounds through sewage treatment plants. Over the past 10 years numerous research articles have been published on the occurrence of human and veterinary pharmaceuticals and personal care products, while, more recently, data have been presented on the occurrence of narcotics. As with many xenobiotics, their eventual sink is the sea or great lakes. The ecotoxicological risk these substances pose to the environment is less clear. Acute risk assessments suggest few examples where the environment is at risk. However, due to the specific mechanisms of these biologically active substances, the chronic long-term risks are less clear. Environmental monitoring is therefore important to better understand the fate and occurrence of these substances to allow better risk assessment and environmental protection. This report addresses the need to better understand the issues associated with human and veterinary pharmaceuticals, narcotics, and personal care products in the environment through performing a review and assessment of existing data and current and planned activities.

On behave of the Norwegian Control Pollution Authority (SFT) the three environmental research institutes IVL (Sweden), NILU (Norway) and NIVA (Norway) have performed a review of the current state of the knowledge on PPCPs and selected compounds prioritised for further monitoring.

The objectives of this report are to:

- Give an overview of the current state of knowledge regarding the occurrence of these compounds in the Nordic environment, and to provide an overview of the environmental effects of PPCPs.
- Recommend which compounds that should be included in future monitoring programs.
- Recommend a sampling strategy together with an indication of analysis possibilities.
- Present an overview of sale volumes for the selected compounds in Norway and the other Nordic countries.
- Present an overview of related projects that are underway or being planned in the Nordic countries and EU, including objective and timeframe.

Occurrence in the Nordic Environment

Only recently several screening and monitoring studies on the environmental occurrence of PPCPs have been performed in the Nordic countries. These studies were funded through both national pollution control authories, the Nordic Council of Ministers, national research councils, and own funding of the research institutes. Some PPCPs, as for example Triclosan, have been measured in a lot of different matrices at different sampling sites in all Nordic countries, thereby giving a reasonably good overview on occurrence and spatial distribution; other compounds are only measured occasionally and a lot of PPCPs have not been measured at all. Due to this variability, it is impossible to give an easy summary of what is measured and what not.

Environmental effects

PPCPs are a rather diverse group of compounds both with respect to their inherent chemical and physical properties and with respect to their desired function and effect as pharmaceuticals or personal care products. The undesired environmental side-effects are similarly diverse: spanning from increasing antibiotic resistance caused by the antibiotics, via cancerogenic/mutagenic/reproductive toxicity to different kind of endocrine disrupting effects as imposex/intersex. It is far beyond the scope of this report to consider all relevant ecotoxicological effects of the assessed compounds.

Recommendations for future monitoring programs

The reviewed compounds were prioritised for further monitoring on the basis of their estimated or known occurrence in the aquatic environment (PEC or MEC), potential to harm aquatic organisms or ecosystems (PNEC), known persistence or bioaccumulation, previously reported occurrence and the analytical chemical possibilities. Since there is a high level of uncertainty associated with the chronic effects associated with these compounds, a precautionary approach has been used.

In the following paragraphs prioritised compounds are listed with decreasing PEC/PNEC-quotient. Furthermore, based on very crude criteria an attempt was made to divide the selected compounds into three groups of different priority:

- Compounds of high priority and with reasonable information on environmental occurrence should be included in regular monitoring programmes (marked with [1] in the following paragraphs).
- Compounds of high and medium priority with no or inadequate information on environmental occurrence should be included in future screening studies (marked with [2] in the following paragraphs).
- Compounds with lowest priority may be included in future screening studies on the base of precautionary principle (marked with [3] in the following paragraphs).

In most cases the environmental effects of the metabolites are not known and it was therefore not possible to perform a risk assessment of the metabolites. However, there are good indications that metabolites may exist in significant concentrations and to give a better understanding of the environmental risk of PPCPs also metabolites should, as long as possible, be included in future screening and monitoring projects

Selected human pharmaceuticals

The one group of human pharmaceuticals for which chronic effects on aquatic organisms are comparatively well understood, are steroid estrogens. Ethinylestradiol, Estradiol, and Estriol have known effects, occur in the aquatic environment, and should therefore be included in a future monitoring programme.

The following group of human pharmaceuticals have been included on the basis of measured effect data and of their risk characterisation suggesting that they may pose a risk to the the Nordic (i.e., Norway and Sweden) aquatic environment:
Estradiol[1], Amoxicillin[2], Penicillin G[2], Ciprofloxacin[1], Ethinylestradiol[1], Propranolol, Paracetamol[1], Fluoxetine[2], Diclofenac[1], Estriol[1], Sertraline[2], Sulfamethoxazole[1], Atorvastatin[2], Naproxen[2], Ibuprofen[1], Allopurinol[2], Amitriptyline[2], Tetracycline[1], Pivmecillinam[2], Ofloxacin[2], Norethisterone[2], Oxytetracycline[1], Erythromycin[2], Carbamazepine[2], Metoprolol[1], Glucosamine[2], Metformin[2], Alendronic acid[3], Verapamil[3], Simvastatin[3], Carvedilol[3], Bicalutamide[3], Oxazepam[3], Paroxetine[3], Trimethoprim[1], Phenoxymethylpenicillin[3], Citalopram[3], Ezetimibe[3], Diazepam[3], Fluticasone[3], Furosemide[3], Midazolam[3], and Clarithromycin[3].

The following group of human pharmaceuticals have been included on the basis of estimated effect data (QSAR) and of their risk characterisation suggesting that they may pose a risk to the the Nordic (i.e., Norway and Sweden) aquatic environment:
Codeine[2], Carisoprodol[2], Acetylcysteine[2], Nifedipine[2], Venlafaxine[2], Dicloxacillin[2], Doxazosin[2], Clindamycin[3], Zolpidem[3], Zopiclone[3], Methenamine[3], Cloxacillin[3], Lymecycline[3], Ampicillin[3], Isosorbide mononitrate[3], Bendroflumethiazide[3], and Bumetanide[3].

Tamoxifen[2] has been included due to its known endocrine disrupting effects since a better understanding of its occurrence is required before it can be safely stated as not posing a risk to the aquatic environment. Warfarin[2] is also used as a pesticide and should therefore be included in future screening programmes.

Some pharmaceuticals are more or less exclusively used in hospitals. However, due to partially lack of application data and of information on environmental effects prioritization is difficult. Iodinated X-ray and Gadolinium-complexed contrast media drugs, cytostatics,

[1] Should be included in regulare monitoring programmes.
[2] Should be included in future screening programmes.
[3] May be included in future screening programmes.

some atypical antipsychotics, radioactive pharmaceuticals, and some anti-viral drugs need to be considered for the screening of hospital effluents.

Selected veterinary pharmaceuticals

The following group of veterinary pharmaceuticals have been included on the basis of measured effect data and of their risk characterisation suggesting that they may pose a risk to the Nordic (i.e., Norway and Sweden) aquatic environment:
Ivermectin[2], Sulfadiazine[2], Fenbendazole[2], Oxytetracycline[1], Amoxicillin[2], Trimethoprim[1], Tylosin[2], Tiamulin[2], Dihydrostreptomycin[2], Penicillin G[2], Enrofloxacin[1], Oxfendazole[2], Doramectin[2], Phoxim[2], Ampicillin[3], Sulfathiazole[3], Ketoprofen[1], Calcium Gluconate[3], Meloxicam[3], Albendazole[3], Praziquantel[3], Flumethrin[3], Spiramycin[3], Doxycycline[1], Permethrin[3], Fipronil[3] and Deltamethrin[3].

The following group of veterinary pharmaceuticals have been included on the basis of estimated effect data (QSAR) and of their risk characterisation suggesting that they may pose a risk to the Nordic (i.e., Norway and Sweden) aquatic environment:
Penicillin procaine[2] (penicillin G + Procaine), Pyrantel[2], Sulfadoxine[2], Phenylbutazone[2], Metamizol[2], Cephalexin[2], Febantel[2], Guaifenesin[2], Clindamycin[2], Flunixin[2], Clavulanic acid[2], Ceftiofur[2], Toltrazuril[2], Benzathine[2], Xylazine[2], and Carprofen[2].

Selected aquaculture pharmaceuticals

A crude ranking of veterinary pharmaceuticals used by the aquaculture industry suggests that further occurrence data are required for Emamectin[1] due to its well-known and high toxicity, and that the following substances should be further evaluated:
Benzocaine[3], Oxolinic acid[3], Praziquantel[3] and Cypermethrin[3].

There is a high level of uncertainty associated with the generated PEC-values for the selected aquaculture pharmaceuticals and it is recommended that a more detailed assessment is performed with refined PEC-data.

Selected personal care products

The ingredients of personal care products are a very diverse group of compounds whose use is not solely restricted to personal care products. The occurrence of certain compounds is well known as are the effects of others (e.g. nonylphenol and Triclosan).

Prioritisation based on risk characterisation has highlighted those that pose the greatest potential risk to the Nordic (i.e., Norway and Sweden) aquatic ecosystems:
Diethylhexyl phthalate[1], Cocoamidopropyl betaine (CADG)[2], Triclosan[1], Sodium lauryl ethersulphate[2], Cetrimonium salts[2], Cocamide DEA[2], Nonylphenol[1], Octamethylcyclotetrasiloxane, Sodium laurylsulphate[2], Dibutyl phthalate[2], Decamethylcyclotetrasiloxane[1], Dimethyl phthalate[2], Octylphenol[1], Butyl methoxydibenzoyl methane[2], Diethyl phthalate[2], EDTA[2], Octamethyltrisiloxane[1], Galaxolide[1], Tonalide[3], Hexamethyldisiloxane[3], Butylparaben[3], Ethylparaben[3], Propylparaben[3], Celestolide[3], Methylparaben[3], Musk ketone[3], Bronopol[3], and Zinc pyrithione[3].

In addition to the above listed compounds, it is proposed that selected sunscreen and insect repellent ingredients are prioritised since they have been shown to occur in the Norwegian aquatic environment, to bioaccumulate in fish and since their effects are largely unknown:
DEET[2], Bayrepel®[2], Benzophenone-3[2], Ethylhexyl methoxy cinnamate[2], Octocrylene[2], and 4-Methylbenzylidene[2].

Selected narcotics

Little or no aquatic toxicity data are available for narcotics, whilst very little occurrence data are available. Uncertainty with respect to consumption volume makes estimation of PECs very difficult. Their reported occurrence in the Norwegian environment is of concern and therefore in order to provide data to evaluate the potential risk narcotics may pose to the aquatic environment, it is proposed that narcotics are prioritised as a group of substances for further evaluation:
Cannabis[2], Opiates[2], Amphetamine[2], Methamphetamine[2], Cocaine[2], and Ecstasy[2].

Sampling and analysis

For both human pharmaceuticals, narcotics and personal care products effluents from waste water treatment plants (WTW) are major sources of emission to the environment. Hospitals, landfill sites and factory emission are also potential sources. All sources should be included in future sampling programmes.

For the land based veterinary pharmaceuticals receiving fields and run-off from farms are major sources. Aquaculture pharmaceuticals on the other hand have emissions directly into receiving waters. These sampling sites should be included in future sampling programmes.

For most of the compounds recommended for future monitoring, analytical techniques have been published and are available.

Final remarks

The compounds listed above represent those compounds that pose sufficient risk to aquatic ecosystems to merit further investigation based on current knowledge as to their occurrence, fate and effects. The number of compounds listed is high, many with widely differing physical-chemical and toxicological properties. This to some extent highlights the absence of data, which results in a high level of uncertainty. This will only be improved through a better understanding of the chronic toxicity of the selected compounds to aquatic organisms and the levels at which aquatic organisms are exposed to these compounds.

2. Sammendrag

Mange tonn human- og veterinærlegemidler blir solgt i Norge hvert år. Videre vet man at store mengder narkotika blir konsumert illegalt. Det omsettes kosmetiske produkter for flere milliarder kroner hvert år. Disse produktgruppene blir ofte omtalt under fellesbetegnelsen PPCP som står for **P**harmaceuticals and **P**ersonal **C**are **P**roducts. I denne rapporten inkluderes også narkotika i begrepet PPCP.

Disse produktene, deres innholdsstoffer og deres metabolitter, ender hovedsakelig i elver, innsjøer, fjorder og i havet enten direkte eller via avløpssystemet og avløpsrenseanlegg. I løpet av de 10 siste årene er det publisert mange forskningsartikler som belyser forekomst av PPCP i miljøet. For kort tid siden ble også forekomst av narkotiske stoffer påvist i miljøet. Selv om man nå vet at mange av disse stoffene ender opp i miljøet, vet man lite om hvilken økotoksikologisk risiko disse stoffene utgjør. Risikovurdering basert på akutt-toksiske effekter indikerer noen tilfeller hvor miljøet kan være i risikosonen. På grunn av den spesielle virkemåten til disse biologisk aktive stoffene, er kroniske langtidseffekter vanskelig å forutse. Måling i miljøet er derfor viktig for å bedre forstå skjebne og forekomst av disse stoffene, noe som er en forutsetning for en bedre risikovurdering og for å kunne iverksette eventuelle tiltak. Denne rapporten belyser nødvendigheten av å øke forståelsen av alle miljøaspekter forbundet med bruken av human- og veterinærlegemidler, narkotika og kosmetiske produkter, og sammenstiller alle tilgjengelige miljødata samt hvilke aktiviteter som er planlagt eller under gjennomføring for tiden.

På oppdrag fra Statens forurensningstilsyn (SFT) har de tre miljøinstituttene IVL (Sverige), NILU og NIVA (Norge) gjennomført en sammenstilling av kunnskapsstatus om PPCP og utarbeidet en prioriteringsliste for videre miljøovervåking av disse stoffene.

Målet med denne rapporten er å:

- gi en oversikt over dagens kunnskap om miljøeffekter av PPCP i Norden.
- gi anbefalinger om hvilke stoffer som bør miljøovervåkes ytterligere, hvilke nye stoffer som bør inkluderes, samt lokaliteter og matrikser som skal inngå i fremtidige overvåkingsprosjekter i Norge og Norden.
- anbefale prøvetakingsstrategier samt analysemuligheter for de foreslåtte stoffene.
- gi en oversikt over omsetningsmengder i Norge og Norden for de anbefalte stoffene.
- gi en oversikt over planlagte eller igangsatte prosjekter relatert til PPCP i Norden og EU.

Forekomst i det nordiske miljøet

I den senere tid har flere screening- og overvåkingsprosjekter av PPCP blitt gjennomført i Norden. Disse studiene er finansiert av både nasjonale forurensingsmyndigheter, Nordisk Ministerråd, nasjonale forskningsfond og ved hjelp av egne instituttmidler. Noen stoffer, som for eksempel triklosan, er blitt målt over mange år, i mange forskjellige prøvetyper og ved mange forskjellige prøvetakingssteder i Norden. For disse stoffene har man etablert en relativt god oversikt over forekomst og fordeling i miljøet, mens man for andre stoffer bare har noen få tilfeldige stikkprøver eller ingen målinger i det hele tatt. Det er derfor umulig å gi en enkel oppsummering over hvilke stoffer som er målt.

Miljøeffekter

PPCP er en gruppe av stoffer med stor variasjon i de kjemisk-fysikalske egenskapene og i funksjonen som legemiddel eller kosmetisk produkt. De uønskete effektene på miljøet varier like mye: De spenner fra økende antibiotikaresistens forårsaket av antibiotika og biocider, via kreftfremkallende/arvestoffskadelige/reproduksjonsskadelige effekter til forskjellige typer hormonhermende effekter som imposex og intersex. Det er derfor ikke mulig i denne rapporten å beskrive alle relevante økotoksikologiske effekter av de undersøkte stoffene.

Anbefalinger for framtidige måleprogrammer

De vurderte stoffene ble prioritert for videre overvåking på basis av deres estimerte eller kjente konsentrasjon i det akvatiske miljøet (PEC eller MEC = **P**redicted eller **M**easured **E**nvironmental **C**oncentration), deres potensiale for å kunne skade akvatiske organismer eller økosystemer (PNEC = **P**redicted **N**o **E**ffect **C**oncentration), deres kjente persistens og bioakkumulerbarhet, tidligere rapportert forekomst og mulighet for å kunne analyseres. Siden det er en høy grad av usikkerhet forbundet med vurderingen av kroniske effekter av disse stoffer er det lagt inn en usikkerhetsfaktor ved beregningen.

I de følgende avsnittene listes de utvalgte stoffene (stoffer med høyest PEC/PNEC-kvotient nevnes først). Stoffene er gruppert etter veldig grove kriterier i tre kategorier:

- Stoffer med høy prioritet og hvor det er relativt god oversikt over forekomst i miljøet. Disse foreslås inkludert i regulære overvåkings-programmer (stoffene er merket med [1]).
- Stoffer med høy og middels prioritet og hvor det er ingen eller dårlig oversikt over forekomst i miljø. Disse foreslås inkludert i framtidige screeningprosjekter (stoffene er merket med [2]).
- Stoffer med lav prioritet. Disse bør inkluderes i framtidige screeningprosjekter på basis av varsomhetsprinsippet (stoffene er merket med [3]).

Miljøeffektene av metabolittene av PPCP er nesten ikke kartlagt og det er derfor heller ikke gjennomført en risikovurdering for metabolittene. På den andre siden har vi gode indikasjoner for at noen metabolitter kan foreligge i signifikante konsentrasjoner og det anbefales at man så langt som mulig inkluderer metabolittene av PPCP i framtidige screening- og overvåkingsprosjekter.

Humanlegemidler anbefalt overvåket

Den eneste gruppen av humanlegemidler hvor kroniske effekter på akvatiske organismer er forholdsvis godt forstått, er østrogener. Etinyløstradiol, Østradiol og Østriol har vist økotoksikologiske effekter, forekommer i miljøet i relevante konsentrasjoner og anbefales derfor inkludert i måleprogrammer.

Følgende gruppe humanlegemidler er anbefalt overvåket på basis av målte effekter og en risikovurdering som tyder på at de over tid kan føre til en risiko for det akvatiske miljøet i Norden (d.v.s. Norge og Sverige):
Østradiol[1], Amoxicillin[2], Penicillin G[2], Ciprofloxacin[1], Etinyløstradiol[1], Propranolol, Paracetamol[1], Fluoksetin[2], Diklofenak[1], Østriol[1], Sertralin[2], Sulfametoksazol[1], Atorvastatin[2], Naproksen[2], Ibuprofen[1], Allopurinol[2], Amitriptylin[2], Tetracyklin[1], Pivmecillinam[2], Ofloxacin[2], Noretisteron[2], Oksytetracyklin[1], Erytromycin[2], Karbamazepin[2], Metoprolol[1], Glukosamin[2], Metformin[2], Alendronsyre[3], Verapamil[3], Simvastatin[3], Karvedilol[3], Bikalutamid[3], Oksazepam[3], Paroksetin[3], Trimetoprim[1], Fenoxymetylpenicillin[3], Citalopram[3], Ezetimib[3], Diazepam[3], Flutikason[3], Furosemid[3], Midazolam[3], og Klaritromycin[3].

Følgende gruppe humanlegemidler er anbefalt overvåket på basis av estimerte effekter (QSAR-beregninger) og en risikovurdering som tyder på at de kan føre til en en risiko for det akvatiske miljøet:
Kodein[2], Karisoprodol[2], Acetylcystein[2], Nifedipin[2], Venlafaksin[2], Dikloksacillin[2], Doksazosin[2], Klindamycin[3], Zolpidem[3], Zopiklon[3], Metenamin[3], Cloxacillin[3], Lymecyclin[3], Ampicillin[3], Isosorbidmononitrat[3], Bendroflumetiazid[3], og Bumetanid[3].

Tamoksifen[2] er anbefalt overvåket på grunnlag av kjente hormonhermende effekter som medfører behov for økt kunnskap om forekomst og spredning i miljøet før man med sikkerhet kan fastslå at det ikke medfører en risiko for det akvatiske miljøet. Warfarin[2] er også brukt som pesticide og anbefales inkludert i screeningprosjekter.

Noen legemidler blir mer eller mindre utelukkende brukt på sykehus. Mangel på gode forbrukstall og informasjon om effekter gjør at en anbefaling av stoffer for overvåking er vanskelig. Ioderte røntgenkontrastmidler og gadoliniumholdige magnetresonanskontrastmidler, cytostatika, noen spesielle psykofarmaka, radioaktive og noen antivirale legemidler burde

[1] Stoff som anbefales inkludert i rutineovervåking.
[2] Stoff som anbefales inkludert i screeningprosjekter.
[3] Stoff som bør inkluderes i screeningprosjekter.

vurderes for screening i avløpsvann fra sykehus.

Veterinærlegemidler anbefalt overvåket
Følgende gruppe veterinærlegemidler er anbefalt overvåket på basis av målte effekter og en risikovurdering som tyder på at de kan føre til en en risiko for det akvatiske miljøet i Norden (d.v.s. Norge og Sverige):
Ivermektin[2], Sulfadiazin[2], Fenbendazol[2], Oksytetracyclin[1], Amoxicillin[2], Trimetoprim[1], Tylosin[2], Tiamulin[2], Dihydrostreptomycin[2], Penicillin G[2], Enrofloxacin[1], Oksfendazol[2], Doramektin[2], Phoxim[2], Ampicillin[3], Sulfatiazol[3], Ketoprofen[1], Kalsiumglukonat[3], Melokicam[3], Albendazol[3], Prazikvantel[3], Flumetrin[3], Spiramycin[3], Doksycyklin[1], Permetrin[3], Fipronil[3] og Deltametrin[3].

Følgende gruppe veterinærlegemidler er anbefalt overvåket på basis av estimerte effekter (QSAR-beregninger) og en risikovurdering som tyder på at de kan føre til en en risiko for det akvatiske miljøet i Norden (Norge och Sverige):
Penicillinprokain[2] (penicillin G + Prokain), Pyrantel[2], Sulfadoksin[2], Fenylbutazon[2], Metamizol[2], Cefaleksin[2], Febantel[2], Guaifenesin[2], Klindamycin[2], Fluniksin[2], Klavulansyre[2], Ceftiofur[2], Toltrazuril[2], Benzatin[2], Xylazin[2] og Karprofen[2].

Veterinærlegemidler brukt i oppdrettsnæringen anbefalt overvåket
En grov rangering av veterinærlegemidlene brukt i oppdrettsnæringen tyder på at en bedre oversikt over forekomst av Emamectin[1] er påkrevd på grunn av dets høye toksisitet. Videre foreslås at følgende forbindelser vurderes nærmere:
Benzokain[3], Oksolinsyre[3], Prazikvantel[3] og Cypermetrin[3].

Estimerte miljøkonsentrasjoner (PEC) for veterinærlegemidler brukt i oppdrettsnæringen er veldig usikre og det anbefales at man gjennomfører en grundigere gjennomgang for å få bedre PEC-verdier.

Stoffer i kosmetiske produkter anbefalt overvåket
Innholdsstoffene i kosmetiske produkter er en veldig uensartet gruppe stoffer. Noen av innholdsstoffene brukes også i andre produkter enn kosmetikk. For noen stoffer har man allerede relativt god oversikt over forekomst og/eller effekter (for eksempel Triklosan eller Nonylfenol).

Følgende gruppe stoffer i kosmetikk er anbefalt overvåket på basis av målte effekter og en risikovurdering som tyder på at de kan føre til en en risiko for det akvatiske miljøet i Norden (d.v.s. Norge og Sverige):
Dietylheksylftalat[1], Cocoamidopropylbetain (CADG)[2], Triklosan[1], Natriumlauryletersulfat[2], Cetrimoniumsalter[2], Cocamide DEA[2], Nonylfenol[1], Oktametylsyklotetrasiloksan[1], Natriumlaurylsulfate[2], Dibutylftalat[2], Dekametylsyklotetrasiloksan[1], Dimetylftalat[2], Oktylfenol[1], Butylmetoksydibenzoylmetan[2], Dietylftalat[2], EDTA[2], Oktametyltrisiloksan[1], Galaksolid[1], Tonalid[3], Heksametyldisiloksan[3], Butylparaben[3], Etylparaben[3], Propylparaben[3], Celestolid[3], Metylparaben[3], Muskketon[3], Bronopol[3], og Sinkpyrition[3].

I tillegg til ovennevnte stoffer foreslås at et utvalg av UV-filtre og insektmidler overvåkes siden disse finnes i miljøet, kan bioakkumuleres og man vet lite om miljøeffektene:
DEET[2], Bayrepel®[2], Benzofenon-3[2], Etylheksylmetoksycinnamat[2], Oktokrylen[2], og 4-Metylbenzyliden[2].

Narkotiske stoffer anbefalt overvåket:
Nesten ingen informasjon om akvatisk toksisitet og om forekomst i miljøet er tilgjengelig for narkotiske stoffer. Usikker informasjonen om forbruk av disse stoffene gjør de estimerte miljøkonsentrasjonene svært usikre. Noen stikkprøver viser forekomst i miljøet i Norge og det foreslås at følgende stoffer vurderes nærmere for framtidig overvåking:
Cannabinoler[2], Opiater[2], Amfetamin[2], Metamfetamine[2], Kokain[2], og Ecstasy[2].

Prøvetaking og analyse

For de fleste PPCP er de kommunale avløpssystemene den største utslippskilden til miljøet. Sykehus, avfallsdeponier og fabrikkutslipp kan også være vesentlige kilder. Alle disse kildene burde inkluderes i framtidige prøvetakingsprosjekter.

For veterinærlegemidler brukt i landbruket er jordene som mottar husdyrgjødsel og avrenning fra jordene og gårdene en vesentlig utslippskilde. Veterinærlegemidler brukt i oppdrettsnæring har utslipp direkte til vann. Disse prøvetakingsstedene burde inkluderes i framtidige prøvetakingsprosjekter.

For de fleste stoffene som er anbefalt overvåket finnes det allerede publiserte kjemisk-analytiske metoder eller metoder som er forholdsvis lett tilgjengelige.

Avsluttende bemerkninger

Stoffene som er anbefalt overvåket representerer de PPCP som kan føre til en risiko for miljøet basert på dagens kunnskap om forekomst, miljøskjebne og effekter. Antall foreslåtte stoffer er veldig høyt og stoffene spriker veldig med hensyn til fysikalsk-kjemiske egenskaper og økotoksisitet. Dette gjenspeiler til en viss grad at man mangler data. Denne situasjonen kan bare forbedres hvis man får en bedre oversikt over den kroniske virkningen av disse stoffene på det akvatiske miljøet og hvorvidt akvatiske organismer er utsatt for disse stoffene.

3. Introduction

Many tonnes of human and veterinary pharmaceuticals are sold in Norway every year, whilst it is estimated that many kilos of narcotics are illegally used. The personal care products market in Norway is worth several billion NOK a year. Most of these xenobiotic compounds and their metabolites end up in rivers, streams and fjords via the sewage network that focuses the excreted and discharged compounds through sewage treatment plants. Over the past 10 years many research articles have been published on the occurrence of human and veterinary pharmaceuticals and personal care products with more recently data being presented on the occurrence of narcotics (PPCPs). The ecotoxicological risk these substances pose to the environment is less clear. Acute risk assessments suggest few examples where the environment is at risk, however due to the specific mechanisms of these biologically active substances the chronic long-term risks are less clear. Environmental monitoring is therefore important to better understand the fate and occurrence of these substances to allow better risk assessment and environmental protection. On the other hand incorporating chronic ecotoxicity testing of aquatic life into assessment strategies is an important step toward increased understanding of environmental effects (Cunningham, 2006).

This report addresses the need to better understand the issues associated with PPCPs in the environment through performing a review and assessment of existing data and current and planned activities.

In the proposal for substances included in future environmental monitoring programmes in Norway and Scandinavia, four groups of high volume chemicals were investigated:

1) Human pharmaceuticals
2) Veterinary pharmaceuticals
3) Components of personal care products
4) Narcotics

Data on sales, consumption and estimated annual use have been retrieved from relevant Norwegian and Swedish authorities. As these four groups of substances differ in the way they are used and circulated in the society, the annual data on consumption and use are associated with very varying uncertainties. For human pharmaceuticals and veterinary pharmaceuticals, high resolution sales data from 2006 for Norway and Sweden were collected. The sale (assumed "consumption" and subsequent environmental emission) of each active compound down to the gram level was reported. For the ingredients of cosmetic substances the corresponding consumption data are based on the annual estimated circulation of the substances or groups of substances (i.e., data on "siloxanes" rather than individual siloxanes). Such data are of course much more uncertain. The consumption of narcotic substances (and subsequent release to the environment) is estimated using a combination of drug prevalence data (based on interviews and social markers) and seizure statistics from the Norwegian and Swedish authorities (Customs and Police). For this particular group the uncertainties regarding the amount released annually to the environment can be expected to be significant.

4. Environmental risk assessment of human and veterinary pharmaceuticals, narcotics, and personal care products

4.1. Introduction

In this chapter the approaches utilised in the present work to assess the environmental effects of HP, VP, PCP and narcotics are presented.

The potential effects exerted by the broad range of compounds studied in this review are wide, ranging from the possible development of resistance towards antibiotics, via cancerogenic/mutagenic/reproductive toxicity, to different kind of endocrine disrupting effects. Due to the specific mode of action of many compounds reported here, they may also have very specific effects (Cunningham et al., 2006). It is far beyond the scope of this report to reconsider all relevant ecotoxicological effects of the assessed compounds. Available data from published literature was used to calculate predicted no-effect concentrations (PNEC) for aquatic organisms. We have not considered other potential release of PPCP, such as sludge application to land, due to the complexity of the overall task. The PNEC is an estimate for the concentration at which potential effects on aquatic organisms and ecosystems might occur for a given compound. Therefore for some compounds where the chronic effects are well known, such as steroid estrogens, there is a greater confidence in the PNEC as it is based on specific effects associated with exposure to estrogenic substances (e.g. induction of the yolk protein vitellogenin in male fish). A review of the aquatic effect data in the peer-reviewed literature shows that acute aquatic effects data are available for some, but by no means all, of the substances reviewed in this project. PNEC is estimated from the acute effect data from the most sensitive test and an assessment factor based on the level of confidence. For a thorough review of how effect data are used to generate PNEC, please see Grung et al., in press. Generally, the reviewed compounds are not acutely toxic. However, there are exceptions to this (e.g. Emamectin). When estimating chronic effects from acute effects the conventional approach has been to extrapolate chronic PNEC from acute data using an acute/chronic ratio (ACR) Although this is a generally accepted approach it is evident that certain human and veterinary pharmaceuticals, narcotics, and personal care products have very high ACRs in fish, e.g. 17α-ethinylestradiol, ACR=150,000; 17β-estradiol, ACR=390,000; Propranolol, ACR= >48,600. However, for other test species such as algae and crustacean, the ACR of the abovementioned compounds is not that high. The result of this complexity is that currently no single assessment factor appears to apply to all aquatic species across a wide range of these compounds.

For other compounds where no effect data are available Quantitative Structure-Activity Relationship (QSAR) or ECOlogical Structure Activity Relationships (ECOSAR) models have been used to estimate the potential effects of each compound ($PNEC_{ECOSAR}$). These modelled data will therefore have the lowest level of confidence.

In this study we have used the PNEC along with predicted environmental concentrations (PEC) to conduct the environmental risk assessment (ERA) for by the reviewed substances. This risk is expressed by a PEC/PNEC or a $PEC/PNEC_{ECOSAR}$ ratio for aqueous environments. We have not considered other toxicities than the aquatic, due to the economical constraints of the project. Where there is an ERA ratio >1 then there is a potential risk to the aquatic environment. The fact that we have used a single assessment factor means that it is entirely possible that compounds with a risk characterisation ratio <1 also pose a potential risk to the aquatic environment since at present we are not aware of any specific chronic effects that these compounds may have. As chronic testing is becoming more frequently incorporated into testing strategies a clearer picture will emerge as to the effects of these compounds on the environment.

The outcomes of ERA for the different groups of compounds studied in this project, is integrated in the relevant chapters below, and a summary is given at the end of each chapter.

4.2. Guidelines

Procedures for conducting ERA on pharmaceuticals are in effect in both Europe and United States (CHMP 2006; USFDA, 1998). The Committee for Medicinal Products for Human Use (CHMP) of the European Pharmaceuticals Evaluation Agency (EMEA) has published guidelines for ERA, which came into effect on the 1st December 2006. An ERA is required for all new marketing authorisation applications for medicinal products. An evaluation of the environmental impact should also be made if there is an increase in the environmental exposure, e.g. a new indication (i.e., the drug is shown efficient in the treatment of a new disease) that may result in a significant increase in the extent of the use. In essence, these guidelines follow the general principle of the ERA procedures as applied to existing and new conventional chemicals in Europe (EU TGD) (European Commission, 2003).

The EMEA guideline (CHMP, 2006) describes how to evaluate the potential risks of the medicinal product to the environment. The guideline is focused only on the environmental risks associated with the use of medicinal products, not risks arising from storage, disposal, synthesis or manufacture of medicinal products. The guideline describes a stepwise tiered procedure for the ERA. The Phase I is a pre-screening assessment aiming at a first estimation of exposure. The Phase I has an action limit of 0.01 µg/L, and if the PEC of surface water is below this limit, it is assumed that the compound is unlikely to represent a risk for the environment. However, in some cases the action limit may not be applicable, for example regarding endocrine disrupting compounds. If the PEC is equal to or above 0.01 µg/L, then a Phase II environmental fate and effect analysis should be performed. Phase II is further divided into an initial prediction of risk based on a dataset of aquatic toxicology and fate (Phase II Tier A). If necessary, an extended risk assessment is performed (Phase II Tier B), where the objective is a substance- and compartment-specific refinement based on an extended dataset on emission, fate and effects.

Information about extent of drug use was retrieved from the Drug Wholesale Statistics Database available at the Norwegian Institute of Public Health. This database includes the total sales of veterinary pharmaceuticals in Norway from all wholesalers in Norway to pharmacies, hospitals and non-pharmacy outlets with the exception of veterinary pharmaceuticals used in aquaculture. The volume of veterinary pharmaceuticals data on wholesales of pharmaceuticals were retrieved for 2006. The following variables were retrieved from the database: number of DDDs, DDD value for each ATC code, number of packages, package size. Based on the sales volume in DDDs and the DDD value the total amounts of the various compound studied were calculated. For compounds without a DDD value, the total amounts of the compounds were calculated by the number of packages sold and package size. For combination products, the content of each pharmaceutical was summarised, and as a result the numbers in the table presented are totals for each pharmaceutical. It was assumed that the entire amount of the veterinary pharmaceuticals sold was used, and that the amount was evenly distributed over the year and throughout the population. For the purposes of this assessment land based agriculture and petcare products have been separated from those substances used in the aquaculture industry.

Regarding veterinary drugs sold in Sweden 2006, sales data were converted to amounts (kg of active substance) by Apoteket AB. Some human pharmaceuticals sold for veterinary applications and administrated to animals were also included. However, the data material did not allow for speciation of the fraction of the active substance being administered to a certain type of animal or aquaculture.

In Norway, limited ERA of pharmaceuticals has not been performed. As a start, the Norwegian Pollution Control Authority has performed a preliminary prioritisation of pharmaceutical compounds (Norwegian Pollution Control Authority, 2005), which was evaluated for possible environmental effect (Grung et al. in press). Based on existing environmental data from the literature, as well as toxicity studies reported, risk quotients for eleven pharmaceuticals could be obtained.

4.3. Estimation of PEC and PEC /PNEC ratios for prioritization of HPs

The PEC in water can be calculated according to the following equation (Sebastine and Wakeman, 2003):

$$\mathrm{PEC}_{\text{surface water}}\left(\mathrm{gL}^{-1}\right)=\frac{\mathrm{A}\times\left(1-\mathrm{R}/100\right)}{365\times\mathrm{P}\times\mathrm{V}\times\mathrm{D}}$$

Where:
A= predicted amount used per year in the relevant geographic area (kg)
R= removal rate (due to loss by adsorption to sludge particles by volatilisation, by hydrolysis, by biodegradation or other specific, naturally occurring processes
P= number of inhabitants of the geographic area considered
V= volume of wastewater per capita and day (m^3), normally between 0.15 and 0.3 m^3 in EU (EMEA default value = 200 l)
D= Dilution of waste water by surface water flow (average factor 10)

Information about the extent of drug use was retrieved from the Drug Wholesale Statistics Database available at the Norwegian Institute of Public Health and from Apoteket AB in Sweden (Cooperation of Pharmacies). The Norwegian database includes the total sales of pharmaceuticals in Norway from all wholesalers in Norway to pharmacies, hospitals and non-pharmacy outlets. Swedish sales data from 2006, in the form of Daily Defined Doses (DDDs) were converted to corresponding masses in kilograms using the WHO definition of a DDD, for each ATC-group (http://www.whocc.no/atcddd/).

Norwegian data on wholesales of pharmaceuticals were retrieved for the year 2006. The following variables were retrieved from the database: number of DDDs, DDD value for each ATC code, number of packages, package size. Based on the sales volume in DDDs and the DDD value the total amounts of the various compounds studied were calculated. For compounds without a DDD value, the total amounts of the compounds were calculated by the number of packages sold and package size. For combination products, the content of each pharmaceutical was summarised, and as a result the numbers in the table presented are totals for each pharmaceutical. Since one active compound can frequently be used in several formulations and combination drugs (thus being represented by several ATC-codes), the total annual sales (consumption) may occasionally be the sum of several ATC-groups. In accordance, the annual sales of one ATC-group may also contribute to the total amount released of several different active components. Furthermore, it was assumed that the entire amount of the pharmaceuticals sold was consumed, and that the amount was evenly distributed over the year and throughout the population. The volume of wastewater per capita per day was assumed to be 200 L, and a dilution factor of 10 was used. Furthermore to assess the worst-case scenario, drug metabolism in humans was disregarded, and the WTW removal rate was set to zero since extensive data on metabolism and removal efficiencies of STP are very rare in the material.

The suggested priority listing of human pharmaceuticals is mainly based upon the reported sales data. When implementing metabolism in the environmental risk assessment of pharmaceuticals, it is very important also to assess the risks possibly associated with the reported metabolites of the drug and investigate whether the drug is being excreted as conjugates (esters of glucoronic acid or sulfonic acid) since these complexes have been reported to disintegrate back to the mother compound in the STP-process.
Regarding STP-removal and the R-factor in the PEC-equation (see above) such reduction of the PEC-value of the drug needs to be substantiated with extensive investigations since the removal in a STP is very dependent of the process technology available at that specific STP, the variation in removal efficiency between different STPs can be significant (Andersson, Woldegiorgis et al. 2006). However, data on human metabolism and STP-removal has been collected throughout the data collection and specific notations have been made in the excel-file compiling all the material.

By collecting ecotoxicological data the highest aqueous concentration of a substance not affecting any aquatic species can be determined. According to the EMEA-guideline, the Predicted No Effect Concentration (PNEC) should be based on data from three trophical levels

(algae, crustaceans and fish). To account for the differences between ecotoxicological testing in the lab and the real environment different assessment factors are used depending on whether the toxicological tests performed are measures of acute or chronic toxicity. In this study a majority of the PNEC-values used are based on ecotoxicological data from the Swedish website www.fass.se, where pharmaceutical companies have transparently published environmentally relevant information on their products. Often, but not always, the ecotoxicological data transparently displayed on fass.se origins from stipulated OECD-testing protocols. The assessment factors used to calculate PNEC from these data can be summarized in Table 1.

Table 1: Assessment factors used to calculate PNEC (OECD).

Available data	**Safety factor**
At minimum one acute assay at one trophic level (Algae, Daphnia or Fish)	1,000
One long-term, chronic toxicity assay (NOEC): with Fish or Daphnia	100
Two long-term, chronic toxicity assays (NOEC) at two trophic levels: Algae and/or Daphnia and/or Fish	50
Two long-term, chronic toxicity assays at three species (NOEC): Algae, Daphnia and Fish (three trophic levels)	10

The total lack of data is a complicating matter concerning the PNEC-values and risk assessment based on the PEC/PNEC-approach. Ecotoxicological data for a substance from three trophic levels is often missing. In cases where the ecotoxicological data is insufficient, an assessment factor 1000 has been used together with the endpoints available. In cases where data is completely missing, QSAR-model predictions of the aquatic toxicity of a substance have been estimated. QSAR-data on ecotoxicity of pharmaceuticals needs to be interpreted and used with great caution. There are few, if any, publicly available QSAR-models developed for the purpose of predicting ecotoxicity of heterogeneous group of compounds such as the human pharmaceuticals. In this study the QSAR-model ECOSAR, originally developed by Meylan and Howard of Syracuse Research Corporation (Meylan 1994; Meylan 1994; Meylan 1995; Meylan 1996) on behalf of EPA (Environment Protection Agency), has been used (http://www.epa.gov/oppt/newchems/tools/21ecosar.htm). The $PEC/PNEC_{ECOSAR}$-priority list constitutes a separate list, and cannot be directly compared to the main PEC/PNEC list. Whether ECOSAR is the most appropriate model to use is indeed questionable. However, in this study, the ranking of pharmaceuticals with no ecotoxicological data is more important than the exact numerical values of the $PEC/PNEC_{ECOSAR}$-quotients.

The calculation of the total amount annually used is for some drugs a challenge. Some formulations of a drug may not have a DDD, e.g. vagitories and transdermal formulations, and may contribute significantly to the total amount of used active substance. To provide an example, a tube of NSAID gel may be used over a period of weeks or months, even though the treatment was scheduled to last only a few of days. To estimate the amount active compound absorbed through the skin, metabolised and subsequently excreted, compared to the amount rubbed of onto textiles and clothes, is a very complex issue. A general conception is that for vagitories and transdermal products such as patches, at least 50 % of the active compound is retained in the carrier after use. Whether the remaining active substance ends up in the environment is dependent on the route and fate of the litter. This implies that the amounts potentially released into the environment may be lower than suggested from the sales figures. Contrary, if a product is incorrectly disposed, e.g., flushed down the toilet; a larger amount may be released into the environment than predicted from sales figures.
Nevertheless, drug metabolism is presumably the most important contribution to the predicted environmental concentrations.
Using Ethinylestradiol, as an example, different outcomes in PEC/PNEC risk quotient is obtained whether a complete estimate of all formulations containing Ethinylestradiol (ca 70 kg) or estimated consumption (ca 4 kg) is used (Data from Sweden, based on WHO-DDD).

Another drawback regarding ERA based on PEC/PNEC-quotients as used in this study is that the PNEC-data for pharmaceuticals are, at the best, based on standard OECD-protocols. These protocols are developed to assess the ecotoxicity of industrial chemicals and aqueous wastewaters. The tests are thus rather unspecific whereas pharmaceuticals have been developed to have a very high specificity. Many human pharmaceuticals can be divided into being either receptor agonist or receptor antagonists; they posses some distinct degree of affinity towards a biological target molecule within the human body. When a pharmaceutical is tested for toxicity towards some aquatic species, one should bear in mind that the species used in the test, for instance a species of algae, may not even express that specific target molecule within its repertoire of receptors. Thus the ecotoxicity test using the algae as test species may only display the non-specific ecotoxicity of the pharmaceutical, *i.e.*, it is highly unlikely that measuring the decrease in growth rate of an algae will correctly display the possible long term effects of e.g. a β-blocker in the aqueous environment. Rather, a test species having a circulatory system that can be up-or down-regulated by agonists or antagonist of adrenergic β-receptors would be more suitable for evaluation of the ecotoxicological properties of the drug or class of drugs.

Finally, from the PEC/PNEC risk quotients of the assessed human pharmaceuticals, priority lists have been assembled. The higher the quotient, the more appropriate it is to include the substance in future environmental monitoring programmes.

4.3.1. Human pharmaceuticals exempted from risk assessment in this study

A subset of ATC-groups is exempted from risk assessment and will hence not be suggested for environmental monitoring (which is in full compliance with the EMEA-guideline). Basically these drugs are based on active substances that can be classed as vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal medicinal products. A list of these compounds is given in the appendix.

4.4. Estimation of PEC and PEC /PNEC ratios for prioritization of VPs

4.4.1. VPs used in agriculture

Both the EMEA- and the VICH-guidelines are rather complex and calculating a PEC for surface water is tedious, time-consuming and requires extensive parameterisation of the data (VICH, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products). The risk assessment procedure is taking different exposure scenarios into account and the procedure have more resemblance to the risk assessment of pesticides than of human pharmaceuticals. The stipulated environmental risk assessment strategy is highly tiered and at first data on type of husbandry is required along with data on how the veterinary pharmaceuticals is administered (fraction of herd that is being treated, dose/bodyweight of treated animals, bodyweight, stocking density of treated animals etc). Furthermore, distinctions in the approach of risk assessment are being made on how the animals/herd is reared, in stables or on a pasture (EMEA/CVMP/05596-Final). In the higher tier approach, a surface water PEC can only be calculated (be derived) from (in order of appearance) PEC (SOIL), PEC (PORE WATER), and PEC (GROUND WATER).

In the case of internally applied pharmaceuticals, a cut-off concentration in manure and fresh dung regulate the need for further assessment. If the concentration of the active compound or major metabolite is found in concentrations below 100 μg/kg (in manure) and in concentrations below 10 μg/kg in fresh dung and no active ingredient or major metabolite is excreted by animal urine on pasture, no further assessment is considered necessary. If substances are degraded with a half-life faster than 30 days after spreading of manure/slurry on land, no further assessment is necessary, even though the concentration of the substance exceeds a concentration of 100 μg/kg (in manure). After the evaluation of the possible exposure routes, with the above mentioned possibilities to stop further assessment, the EMEA document prescribe that further assessment is needed, as described in a phase II decision tree, only if the PEC in groundwater and soil exceed 0.1 μg/L and 10 μg/kg, re-

spectively. A specific higher tier approach is applicable to aquaculture.

Instead of the aforementioned approach, Swedish and Norwegian sales data were used in combination with ecotoxicological data, when available, and data on veterinary drugs from the human pharmaceuticals study.

4.4.2. VPs used in aquaculture

Aquaculture in Norway is mainly focused on the Western and Northern Coast of Norway where there are 1 189 regulated faculties. Using the sales data from the Drug Wholesale Statistics Database available at the Norwegian Institute of Public Health PECs were calculated for the veterinary pharmaceuticals used in Norwegian fish farms (Table 14). The PECs were calculated using the following simple equation:

$$PEC_{surface\ water}\left(gL^{-1}\right) = \frac{N \times V \times A}{D}$$

Where:

N= Number of production facilities (1189)

V= Volume of water used (12 000 m^3)

A= predicted amount used per year at the facility (kg)

D= Dilution of waste water by surface water flow (average factor 100)

Finally, from the PEC/PNEC risk quotients of the assessed veterinary pharmaceuticals, priority lists have been assembled. The higher the quotient, the more appropriate it is to include the substance in future environmental monitoring programmes.

4.5. Estimation of PEC and PEC /PNEC ratios for prioritization of personal care products

For calculating PECs for personal care products Swedish consumption data from 2006 given in the SPIN database together with measured environmental concentrations (MEC) has been used.

Finally, from the PEC/PNEC risk quotients of the assessed personal care products, priority lists have been assembled. The higher the quotient, the more appropriate it is to include the substance in future environmental monitoring programmes.

4.6. Estimation of PEC and PEC /PNEC ratios for prioritization of narcotics

For calculating PECs for illegal narcotics, the prevalence of drug use in Norway was used. This is estimated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (http://www.emcdda.europa.eu). The "prevalence of drug use for the last year reported" was collected from this site, and for opiates it was collected from the UN drug report 2007 (UNODC, 2007). The prevalence is given as % of the population in the age group 15-65 years (EMCDDA), and is converted to the number of users based on the population in Norway in 2006 (http://www.ssb.no). The average quantity of drug used at a typical drug use episode is from the Home Office Online report (2006) and is based on numbers from Australian users. The quantity used for heroin is based on a Norwegian study (Bretteville-Jensen, 2005). The estimated weight of typical drug dose is also from the Home Office report (2006). The purity of drugs is based on the purity of seized drugs. These data are retrieved from Kripos (Narkotikastatistikk 2006, http://www.politi.no). All these information give the basis for an estimation of how much drug was used in Norway during 2006. The PECs are estimated the same way as the pharmaceuticals, and are corrected for metabolism in the table.

5. Human pharmaceuticals (HP)

5.1. Introduction

The sale and use of human pharmaceuticals (HPs) has gradually increased over time worldwide. In Norway, the annual growth, measured in the number of defined daily doses (DDDs), has varied from 1 to 8% in the period 1993-2006 (Norwegian Institute of Public Health, 2007). Over the past years the environmental concern on pharmaceuticals have increased. Wastewater treatment plant (WTP) effluents have been identified as a major source of these compounds in the environmental, due to poor removal of many compounds. As a consequence, variable quantities of pharmaceuticals reach surface waters, groundwater and sediments, ranging in concentrations from nanograms to micrograms per litre. (Kümmerer, 2001). Pharmaceuticals can be degraded in the environment by biotic and/or abiotic processes, but may cause persistent exposure due to their continuous infusion into aquatic media via STP effluents (Castiglioni et al., 2006; Vieno et al., 2007). Due to the large amounts of pharmaceuticals released into the environment and their intrinsic properties to cause biological effects, the risks they present to the environment cannot be ignored (Fent et al., 2006).

5.2. Environmental occurrence, fate, and effects of human pharmaceuticals

In 2006, there were 1414 approved human pharmaceuticals on the Norwegian market. It is beyond the mandate of this project to discuss all these compounds regarding their relevance for implementation in future monitoring programs. The HPs are presented according to their ATC coding (as stipulated by WHO). The medical relevance of each subclass is briefly discussed as an introduction in each section. Sales ranking, if included, is based on data for 2006 and is in the text abbreviated as DDD, i.e. DDD per 1000 inhabitants per day.

However, some of these compounds have been successfully identified in the Nordic environment, and they will be presented in the present chapter. The location and the matrix they were identified in will be presented. Several screening studies have been performed in Norway, Sweden, and Finland. From Denmark, only a few reports exist, and these focus mainly on antibiotics that are extensively used in the economically important swine and bovine farming industry. No monitoring for PPCPs has been performed in Iceland (Personal communication, Dr. E. G. Gudmundsdottir, Environmental Regulation, Iceland). No information has been obtained from the Faeroe Islands and Åland. Detailed descriptions of the prioritised compounds are given in separate boxes and includes ATC and CAS numbering, structure, MW, pKa, log P and/or log D. Log D is only relevant for ionisable compounds and log D values are only covered in the environmentally relevant range of pH 5 to 8.

Some important metabolites and their relevance are discussed in the text. A complete survey of metabolites alone would require a further literature study comparable to the present study. Several complicating factors contribute to this. In some cases the structure of the metabolites is not known. For some drugs several metabolites resulting from both phase I and II reactions are formed. Furthermore, bacterial degradation of drugs in the sewage is a poorly covered field, but it must be expected that bacterial degradation pattern for the individual drug do not resemble eukaryotic degradation. Finally, photo-chemical degradation will also contribute significantly to the degradation complexity (Khetan and Collins 2007). For these reasons, only human metabolism is included for the pharmaceuticals.
Any known environmental effects of the parent drug will be provided along with persistence and bioaccumulation potency, if available. The ERA results, that is, the estimated PEC/PNEC or $PEC/PNEC_{ECOSAR}$ will be presented and used as basis to discussion whether a compound is recommended implemented in future monitoring programs.

Prioritisation of HPs for further monitoring is based on (1) environmental risk characterisation (ERA) using measured or estimated effects, (2) compounds measured in in the environment in relevant concentrations or (3) very persistent compounds with an uncertain environmental effect, and (4) sales number or amount sold.

Finally, the utilised sample preparation and instrumental detection are described in the text for the monitored compounds. Proposed analytical strategy for hitherto not analysed compounds (in the Nordic environment) will be presented at the end of the chapter.

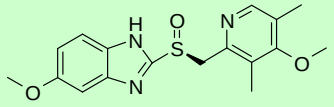
5.2.1. A Alimentary tract and metabolism

A02B Drugs for Peptic Ulcer and Gastro-Oesophageal reflux disease

Relevant substances: mode of action and pharmacokinetics

Peptic ulcers are treated by two major drug regimens, by the old H_2-receptor antagonist (A02BA) and the newer proton pump inhibitors (A02BC). **Omeprazole** and its optically pure S-enantiomer **Esomeprazole** belong to the latter class. Their mechanism of action involves an acid mediated rearrangement of the molecule that in turn irreversibly inhibit the H^+/K^+-ATPase by covalent binding (Williams and Lemke 2002). **Omeprazole** is completely oxidised by CYP2C19 after absorption (Tørisen 2007). In 2006, **Esomeprazole** was ranked 17th by DDD turn over (Tørisen 2007). **Omeprazole** and **Esomeprazole** should be regarded as one compound as it will be very challenging to separate the two enantiomers.

(Es)omeprazol



A02B C01
(es): A02BC05, 119141-88-7
$C_{17}H_{19}N_3O_3$ S, Mw=345.4
pKa=4.72 and 8.46, log D= 2.10

Results from previous screenings

In Norway, **Omeprazole** was not detected influent and effluent STP water, sludge and sediment at several locations (Møskeland 2006). Furthermore, Omeprazole was not detected in biota (Møskeland 2006). One explanation to this lack of successful detection is attributed to the extensive metabolism **Omeprazole** undergoes. Any future monitoring programs involving Omeprazole (and other proton pump inhibitors) should rather include the major metabolites than the parent compound.

Relevant environmental properties, ERA, and monitoring recommendations

The environmental effects of the metabolites are not known (Läkemedelsindustriföreningen 2007; NIH 2007). The PEC/PNEC for **Omeprazole** is 0.0005 (Norway; N) and 0.008 (Sweden; S), whereas the PEC/PNEC for the metabolites is not known. It is not recommended to include Omeprazole in future monitoring programs.

Analytical strategy

Aqueous samples underwent solid phase extraction (SPE) and solid samples liquid-liquid extraction (LLE) with MeOH prior to liquid chromatography mass spectrometry (LC-MS) analysis (Møskeland 2006). It is probably difficult to separate Omeprazole and Esomeprazole during analysis, and these two compounds should be regarded as one.

5.2.2. B Blood and blood forming organs

Relevant substances: mode of action and pharmacokinetics

The anti thrombotic agent **Warfarin** (B01AA03) is also used as a pesticide and the calculated PEC-value herein may therefore be an underestimation.

Results from previous screenings

No compounds from this group have been monitored in the environment.

Relevant environmental properties, ERA, and monitoring recommendations

Warfarin has a log Kow of 2.70 and a water solubility of 17 mg/l, which indicate that **Warfarin** is expected to adsorb to suspended solids and sediment; however, the potential for bioconcentration in aquatic organisms is low. **Warfarin** hydrolyses very slowly in water with a half-life (pH 7, 25°C) of 16 years (NIH 2007). The PEC/PNEC of **Warfarin** is 0.003 (N) and 0.002 (S), but is probably underestimated, as it is extensively used as a pesticide. **Warfarin** is recommended to be monitored in the future.

Analytical strategy

SPE followed by LC-MS can be used to analyse Warfarin.

5.2.3. C Cardiovascular system

C03 Diuretics

Relevant substances: mode of action and pharmacokinetics

Diuretics are important in the treatment of hypertension by stimulating increased excretion of water and electrolytes, which in turn decreases the cardiac workload. High ceiling (or loop) diuretics have high potency and inhibit the $Na^+/H^+/2Cl^-$ symport in the loop of Henle in the kidneys. **Furosemide** (C03CA01) is excreted primarily unchanged (Williams and Lemke 2002), and was ranked 14th (by DDD turn over) in 2006 in Norway.

Results from previous screenings

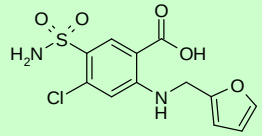
Furosemide has been monitored once in Norway, and was detected in both STP influent and effluent water, and even in surface water (Møskeland 2006). No **Furosemide** was detected in sludge or sediment, which is in accordance with the calculated log D= -0.09 at pH 7.

Relevant environmental properties, ERA, and monitoring recommendations

Furosemide is slowly degraded in the environment (Läkemedelsindustriföreningen 2007), and its environmental effect is unclear. The pKa_2 of **Furosemide** is 7.5, indicating that this compound will partially exist in the protonated form in the environment and cations generally adsorb to organic carbon and clay more strongly than their neutral counterparts. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low (NIH 2007).

The PEC/PNEC calculated in the present study was 0.01 (N) and 0.02 (S). **Furosemide** may be implemented in future monitoring programs.

Furosemide



C03CA01, 54-31-9
$C_{12}H_{11}ClN_2O_5S$, Mw=330.7
pKa=3.04, log D= -0.09

Analytical strategy

Furosemide was isolated from aqueous matrices by SPE and from solid matrices by methanolic LLE, followed by LC-MS (Møskeland 2006).

C07 Beta Blocking Agents

Relevant substances: mode of action and pharmacokinetics

Beta-blockers are high volume drugs used to treat hypertension. Their mechanism of action is lowering blood pressure through their competitive inhibition of cardiac and vascular β_1 and β_2 receptors thereby reducing the contractility of the myocardium and decreasing the heart rate (Williams and Lemke 2002). Metabolism varies greatly within the group, the (renal) excretion of unchanged drug is from 1% (**Propranolol** and **Acebutol**), 15% (**Metoprolol**) to 100% (**Sotalol** and **Atenolol**) (Tørisen 2007).

Results from previous screenings

Metoprolol (C07AB02) was detected in STP influent and effluent water in Finland (Vieno, Tuhkanen et al. 2006), Norway (Weigel, Berger et al. 2004; Thomas, Langford et al. 2007), and Sweden (Bendz, Paxeus et al. 2005), in river water in Finland (Vieno, Tuhkanen et al. 2006), and in hospital effluent water in Norway (Thomas, Langford et al. 2007). The effluent water from a manufacturing plant in India contained high concentrations of **Metoprolol** (Larsson, de Pedro et al. 2007). **Atenolol** (C07AB03) has only been detected in STP influent and effluent water, and in river water in Finland (Vieno, Tuhkanen et al. 2006). **Acebutol** (C07AB04) is not available in Norway (Tørisen 2007), but has been detected in STP influent and effluent water, as well as in river water in Finland (Vieno, Tuhkanen et al. 2006). **Sotalol** (C07AA07) has only been reported to be present in STP in- and effluent, as well as river water in Finland (Vieno, Tuhkanen et al. 2006). **Propranolol** (C07AA05) is reported to be present in STP influent and effluent water in Norway (Weigel, Berger et al. 2004) and Sweden (Bendz, Paxeus et al. 2005). Finally, **Propranolol** has been detected at concentrations in the same range or above PNEC.

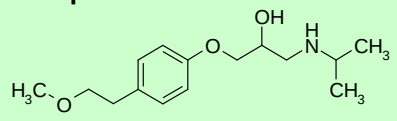
Relevant environmental properties, ERA, and monitoring recommendations

Most β-blockers are lipophilic, thus having the potential to bioaccumulate. The effects of metabolites are not known.

Metoprolol is reported to be toxic towards the

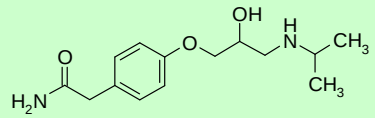
green algae *Selenastrum capricornutum*, and **Sotalol** towards *Daphnia magna*.
Metoprolol PEC/PNEC is 0.2 (N) and 0.03 (S), for **Atenolol** 0.04 (N) and 0.01 (S), **Sotalol** 0.002 (N and S). No information about the effects of **Atenolol** was found, however, due to structural similarity, it is expected that **Atenolol** may cause the same effects as the other β-blocking agents.

Metoprolol



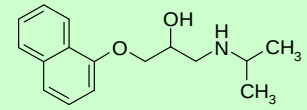
C07A B02, 51384-51-1
$C_{15}H_{25}NO_3$, Mw=267.4
pKa=9.7, log P=1.69

Atenolol



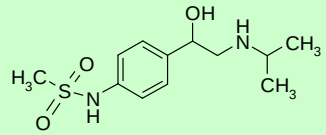
C07A B03, 29122-68-7
$C_{14}H_{22}N_2O_3$, Mw=266.3
pKa=9.6, log P= 0.16

Propranolol



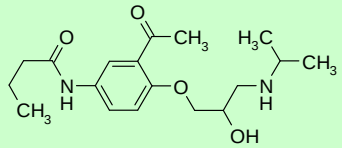
C07A A05, 525-66-6
$C_{16}H_{21}NO_2$, Mw=259.4
pKa=9.14, log D=1.0

Sotalol



C07A A07, 959-24-0
$C_{12}H_{20}N_2O_3S$, Mw=272.4
pKa=9.55, log P= 0.24

Acebutolol



C07AB04, 34381-68-5
$C_{18}H_{28}N_2O_4$
Mw=336.4 pKa=9.2,
log P=1.71

Propranolol (CAS 525-66-6) is reported to be toxic towards *O. latipes*. For **Propranolol** a LOEC (4 weeks, *Oryzias latipes*) reproduction= 0.5 µg/L is reported, and PEC/PNEC is 21.5 (N) and 33.1 (S), making it an obvious candidate for future monitoring. The annual consumption of the substance was approximately 1.1 tonnes in Sweden and 367 kg in Norway 2006. For **Propranolol** specific experiments have in fact been performed on fish where **Propranolol** was injected in the blood stream of the fish while monitoring the fish heart beat. Initially the fish were exposed to a very high concentration of **Propranolol** (70.9 µg/L) during 48 h while no effects on heart rate were found. After a subsequent intravenous injection of **Propranolol**, heart rate remained unaffected in pre-exposed fish but was significantly lowered in naïve fish. The study suggests that physiological systems under homeostatic control, like heart rate, may not be particularly sensitive despite being direct targets (Larsson et al., 2006). From the risk quotient data **Metoprolol** also appears to pose a threat to the aquatic environment, however **Metoprolol** MEC data suggests that the risks are an order of magnitude lower than **Propranolol** (Thomas et al., 2007).

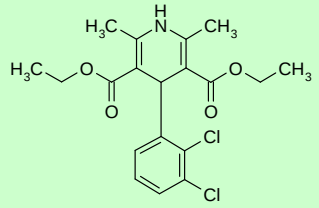
Analytical strategy
SPE combined with LC-MS has been used to identify the beta blocking agents.

C08 Calcium Channel Blockers
Relevant substances: mode of action and pharmacokinetics
The mode of action of calcium channel blockers or calcium antagonists is by competitive blocking of Ca^{2+} migration through Ca-channels and thus altering the cardiac action potential. **Felodipine** (C08CA02), the only monitored compound from this group, undergoes extensive oxidative first pass metabolism by CYP3A4, and no known active metabolites are known (Williams and Lemke 2002). **Verapamil** undergoes first pass metabolism and more than 90 % is bound to plasma proteins. It is metabolized in liver to more than 12 different metabolites, one of them, Norverapamil, has 20% of the activity of **Verapamil**.

Results from previous screenings
Felodipine has been detected in sludge, but it was not detected in STP water and biota (Møskeland 2006). This pattern is presumably due to the high log P of **Felodipine**.
Verapamil has not been monitored in the Nor-

dic environment, however, it has been detected in e.g. Germany (Hummel, Loffler et al. 2006).

Felodipine



C08C A02, 72509-76-3
$C_{18}H_{19}Cl_2NO_4$, Mw=384.3
pKa=2.73,
log P=4.83

Relevant environmental properties, ERA, and monitoring recommendations

Verapamil (C08DA01) is another Ca-antagonist is reported to greatly increase the toxicity of other xenobiotics, as it inhibits the action of P-glycoprotein-like transporters, a common detoxifying mechanism among living organisms (Daughton and Ternes 1999). The PEC/PNEC is 0.068 (N) and 0.040 (S). **Verapamil** should be considered implemented in future monitoring programs.

Analytical strategy

SPE (water samples) or LLE (solid samples) followed by LC-MS was utilised to identify **Felodipine** and **Verapamil**.

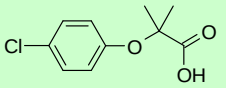
C10 Lipid Modifying Agents

Relevant substances: mode of action and pharmacokinetics

The fibrates, e.g. **Bezafibrate** (C10AB02) and **Clofibric acid** (C10AB) reduce VLDL (very low density lipoprotein) concentrations in the blood by stimulating lipoprotein lipase, the enzyme responsible for removing triglycerides from plasma. High concentration of VLDL is associated with coronary heart disease. Fibrates are not sold in Norway in 2007 (Tørisen 2007).

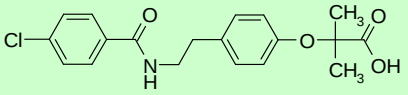
Statins (or HMG-CoA reductase inhibitors) form a class of hypo-lipidemic agents, used to lower cholesterol levels in people with or at risk of cardiovascular disease. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Statin consumption in Norway is high with tonne quantities being consumed annually. **Simvastatin** (C10AA01) and **Atorvastatin** (C10AA05) were ranked 1st and 4th in DDD turn over in 2006 in Norway (Tørisen 2007).

Clofibric acid



C10A B01, 882-09-7
$C_{10}H_{11}ClO_3$, Mw=214.7
pKa= 3.5, log P/D=-0.76

Bezafibrate



C10AB02, 41859-67-0
$C_{19}H_{20}ClNO_4$, Mw=361.83
pKa=3.61, log D=0.03

Results from previous screenings

Bezafibrate was detected in STP influent in Finland (Lindqvist, Tuhkanen et al. 2005). Weigel et al. screened for **Clofibric acid** (C10AB01) in STP and sea water in Norway, but the compound was not detected (Weigel, Berger et al. 2004).

NIVA has detected **Simvastatin** in samples collected from Swedish and Norwegian STPs (Barron, unpublished data) and they have been detected in Canada (Miao and Metcalfe 2003).

Relevant environmental properties, ERA, and monitoring recommendations

Clofibric acid is regarded as one of the most persistent drug residues with an estimated persistence in the environment of 21 years (Khetan and Collins 2007). However, as fibrates are not sold in Norway, it is not recommended to include it in future monitoring programs.

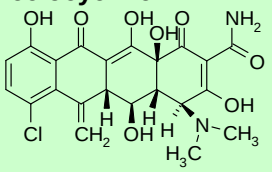
Due to a log Kow of 4.68 **Simvastatin** is expected to adsorb to suspended solids and sediment. An estimated BCF of 800 suggests the potential for bioconcentration in aquatic organisms is high (NIH 2007). Risk characterisation of statins suggests that **Atorvastatin** (CAS 134523-00-5) and **Simvastatin** (CAS 79902-63-9) should be selected for monitoring in Norway; their PEC/PNEC are 0.066 (N) and 0.053 (S) for **Simvastatin** and 1.95 (N) and 0.686 (S) for **Atorvastatin.** Statins are extensively metabolised and their environmental effects are largely unknown (Khetan and Collins 2007).

Analytical strategy
SPE followed by derivatisation and gas chromatography mass spectrometry (GC-MS) was employed for the analysis of fibrates.
Statins were detected in by SPE and LC-MS.

5.2.4. D Dermatologicals

D10 Anti-Acne Preparations
For details regarding mechanisms of action, please confer section J01A below.
Meclocycline (D10AF04) is not sold in Norway, and hence it was not detected in hospital effluent and STP influent and effluent water in Norway (Thomas, Langford et al. 2007).

Meclocycline



D10A F04, 2013-58-3
$C_{22}H_{21}ClN_2O_8$, Mw=476,8743
pKa=4.5, log D=-2.59

No other dermatologicals have been monitored in the Nordic environment. They do not show high PEC/PNEC-scores and are therefore not prioritised for future screening

5.2.5. G Genito-urinary system and sex hormones

Relevant substances: mode of action and pharmacokinetics
Sex hormones are used as contraceptives and in hormone replacement therapy during the menopause. In both cases, some of the administered hormones are produced naturally in the female body, that is, **Progesterone**, **Estradiol**, **Estrone** and **Estriol**. Xenobiotic hormones are administered to obtain effects similar to the endogenous hormones, and include **norethindrone** and **17α-ethinylestradiol**. In Norway in 2006, **Levonorgestrel** was the contraceptive with the highest turnover; however no reports exist where this compound has been monitored in the Nordic environment.

Results from previous screenings
The four natural hormones have been monitored in the Nordic environment, along with the non-natural hormones **norethindrone** and **17α-ethinylestradiol**. All hormones are ubiquitous in the Nordic environment, which is expected considering their natural occurrence. In Norway and Sweden, **Estradiol, Ethinylestradiol, Estriol** have been detected at concentrations in the same range or above PNEC (Andersson, Woldegiorgis et al. 2006; Møskeland 2006; Thomas, Langford et al. 2007).

Relevant environmental properties, ERA, and monitoring recommendations
The hormones are hydrophobic, which is reflected in their high log P values. It is therefore not surprising that the hormones are found in higher concentrations in particulate matter, such as sludge, compared to the aqueous phase. No data exist on the concentration of this group in biota, but the substances have the potential to bioaccumulate having log Kow>3.
The biological effects of these hormones on aquatic organisms are indeed issues of considerable concern (Khetan and Collins 2007). This is also reflected by their relatively high PEC/PNEC-scores; 31.3 (N) and 28.5 (S) for **Ethinylestradiol**, 3.5 (N) and 6.5 (S) for **Estriol**, and 0.22 (S) for **Estradiol**. Estrogens constitute a very potent group of substances for which environmental effects have been observed in the aquatic environment, especially fish and amphibians (feminisation of the male population). The effect concentrations for estrogens are very low (< 1 ng/l). Due to the use of an effective biomarker with very high specificity (the induction of vitellogenin production in fish) the assessment of the risk associated with estrogens is probably the most accurate of all pharmaceuticals. The individual drug chosen for monitoring in Sweden from this group is **Ethinylestradiol** (CAS 57-63-6), predominantly used in contraceptive products. In Norway it is recommended to monitor for **Ethinylestradiol**, **Estradiol** and **Estriol**. The annual consumption of **Ethinylestradiol** in 2006 was approximately 70 kg in Sweden and 2 kg in Norway. There are differences between sold amounts for several compounds between Norway and Sweden. To explain and interpret these differences is beyond the scope of the present work, as such explanations are demanding. No data on biodegradation properties of **Ethinylestradiol** was found in the literature,

however the structural analogue **Estradiol** was reported not readily degradable, having a $t_{½}$ of 7 d (OECD 301C), and a $t_{½}$ of 10 d during photolysis (Läkemedelsindustriföreningen 2007). From the PEC/PNEC-list, also **Estriol** (CAS 50-27-1) seems reasonable to include in a monitoring study. It has generally a higher estrogenicity than **Estradiol** but not as high as **Ethinylestradiol** (estriol is however less potent as an endocrinic disruptor in fish, compared to estradiol). However, **Estriol** is an endogenous estrogen that is being excreted from humans also in populations where no drug is sold (and also being excreted from most vertebrate species). Thus, a background concentration of **Estriol** can be expected in environmental samples making this substance less suitable for monitoring.
For **Levonorgestrel** and some other progesterones used either alone or together with estrogens, no PEC/PNEC is estimated due to the lack of data.

Analytical strategy
Sample preparation of water samples is normally done by SPE and by liquid extraction from freeze-dried solid samples. Either LC-MS or GC-MS is used to identify and quantify these compounds (Andersson, Woldegiorgis et al. 2006; Møskeland 2006; Thomas, Langford et al. 2007).

5.2.6. H Systemic hormonal preparations, excluding sex hormones and insulins

No drugs from ATC group H have been monitored in the Nordic environment.

It is worth mentioning that **Levotyroxine sodium** (H03A A01) is ranked 15th by DDD turn over (2006) (Tørisen 2007), but no PEC/PNEC is available.

5.2.7. J Anti-infectives for systemic use

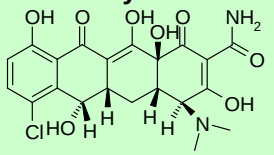
Antibacterials are conveniently termed as bactericide (kills bacteria) or bacteriostatic (prevents bacterial breeding).

J01A Tetracyclines
Relevant substances: mode of action and pharmacokinetics
Tetracyclines are a group of broad-spectrum antibiotic produced by the *Streptomyces* bacterium, indicated for use against many bacterial infections. Tetracyclines are highly functionalised and partially reduced naphtacenes. Tetracyclines bind to 30S ribosomal subunit and hence inhibit binding of aminoacyltransferRNA to 30S, resulting in termination of peptide chain growth (Williams and Lemke 2002). Because resistance is widespread, these once extremely popular antibiotics are now falling into comparative disuse (Williams and Lemke 2002). Tetracyclines undergo little or no metabolism and is largely excreted unchanged through urine or faces.

Results from previous screenings
Tetracyclines are extensively monitored.
Demeclocycline (J01A A01) has been detected in STPs and hospital effluents in both Norway and Sweden (Andersson, Woldegiorgis et al. 2006; Thomas, Langford et al. 2007), and in Sweden in manure from animal keeping farms (Andersson, Woldegiorgis et al. 2006).
Doxycycline (J01A A02) has been detected in Denmark in swine manure (Jacobsen and Halling-Sørensen 2006), but not in Sweden (Andersson, Woldegiorgis et al. 2006). In Norway and Sweden it was detected at STPs and hospital effluent water, and in Sweden also in leachates from deponies (Dye, Remberger et al. 2006; Thomas, Langford et al. 2007).
Tetracycline (J01A A07) has been detected in Sweden in STP influent and effluent water, sludge, manure from animal keeping farms, and leachate (Andersson, Woldegiorgis et al. 2006). In Norway **Tetracycline** has been detected in STPs and hospital effluent water (Thomas, Langford et al. 2007) and in sludge (Dye, Remberger et al. 2006; Thomas, Langford et al. 2007). A Danish study reported the presence of **Tetracycline** in swine manure (Jacobsen and Halling-Sørensen 2006).
Oxytetracycline (J01A A06) is also used as a veterinary pharmaceutical and has been detected in Denmark in swine manure (Jacobsen and Halling-Sørensen 2006). A Swedish study reported successful detection of **Oxytetracycline** from STP in- and effluent water, sludge, and in manure from animal keeping farms (Andersson, Woldegiorgis et al. 2006). STP and hospital effluent water in Norway also

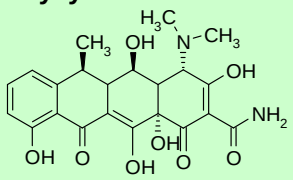
contained **Oxytetracycline** (Thomas, Langford et al. 2007).

Demeclocycline



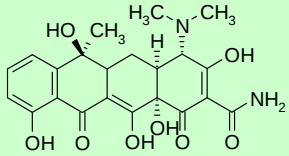
J01A A01, 127-33-3
$C_{21}H_{21}ClN_2O_8$, Mw=464,8631
pKa=4.50; 11.0, log P=-0.87

Doxycycline



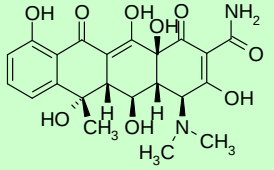
J01A A02, 564-25-0
$C_{22}H_{24}N_2O_8$, Mw=444.4
pKa=3.02; 7.97; 9.15, log P=0.024

Tetracycline



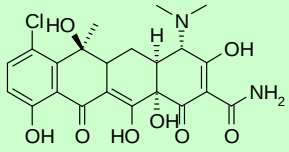
J01A A07, 2058-46-0
$C_{22}H_{24}N_2O_8$, Mw=444.4
pKa=3.32; 7.78; 9.58, log P= 1.131

Oxytetracycline



D06A A03, D07C A01, **J01A A06**, S01A A30, S03C A042, 2058-46-0
$C_{22}H_{24}N_2O_9$, Mw=460.4
pKa=3.22; 7.46; 8.94, log P= 0.890

Chlorotetracycline



57-62-5
$C_{22}H_{23}ClN_2O_8$, Mw=478.9
pKa=3.33; 7.55; 9.33, log P= 0.360

Chlortetracycline (J01A A03) has been detected in swine manure in Denmark (Jacobsen and Halling-Sørensen 2006), leachate, STP in- and effluent as well as hospital effluent water in Sweden (Andersson, Woldegiorgis et al. 2006), in hospital effluent in Norway (Thomas, Langford et al. 2007).

Tetracycline and **Oxytetracycline** have occasionally been detected at concentrations in the same range or above PNEC.

Relevant environmental properties, ERA, and monitoring recommendations
The environmental effects of these chemically closely related compounds are exemplified by **Tetracycline**. For the green algae *Pseudokirchneriella subcapitata* an EC_{50} over 72 h was 0.31 mg/L by the OECD 201 method, and a NOEC of 0.1 mg/L. Similarly, by OECD 202 for *Daphnia magna*, a LC_{50} over 48 h was estimated to 11 mg/L, and a NOEC of 2.0 mg/L (Läkemedelsindustriföreningen 2007). **Tetracycline** is potentially persistent as it is slowly degraded in the environment; only 1% was degraded after 28 d (OECD301F) (Läkemedelsindustriföreningen 2007) and the PEC/PNEC has been calculated for two tetracyclines: **Tetracycline** 1.000 (N) and 0.390 (S), **Oxytetracycline** 0.464 (N) and 0.194 (S), and these are recommended for future monitoring. The annual consumption (2006) of these substances was approximately 0.81 and 0.26 tonnes in Sweden and Norway, respectively.

Analytical strategy
The Tetracyclines were identified from water by SPE followed by LC-MS, and from solid samples either by LLE (Andersson, Woldegiorgis et al. 2006; Dye, Remberger et al. 2006; Thomas, Langford et al. 2007) or ASE (Jacobsen and Halling-Sørensen 2006).

J01C Beta-lactam antibacterials, penicillins
Relevant substances: mode of action and pharmacokinetics
Beta-lactam antibacterials work by inhibiting enzymes processing the development of the peptidoglycan layer in both Gram positive and negative bacteria.

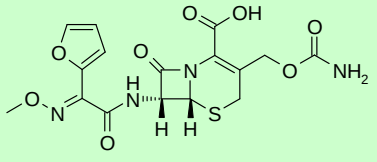
Results from previous screenings
The compounds of this ATC class have not been monitored in the Nordic environment.

Relevant environmental properties, ERA, and monitoring recommendations
The individual drug chosen for monitoring in both Norway and Sweden from this group is **Amoxicillin** (CAS 26787-78-0), due to the high PEC/PNEC score of 148.8 (N) and 11.1 (S). See also the section on "veterinary pharmaceuticals selection for environmental monitoring" below. The annual human consumption of the substance was approximately 2 tonnes in Norway and 5.8 tonnes in Sweden 2006. Other penicillin antibiotics are not recommended for further study since they have a low environmental persistence (Läkemedelsindustriföreningen 2007). The BCF of amoxicillin is 1.0, hence the potential for bioconcentration is low. The water solubility is 0.62 g/L at pH 7, which increases to 640 g/L at pH 10 (ACS 2006).

Analytical strategy
From aqueous samples, SPE combined with LC-MS is the method of choice.

J01D Other Beta-Lactam Antibacterials
Relevant substances: mode of action and pharmacokinetics
Cefuroxime (J01D C02) belongs to the second generation of cephalosporins. A cephalosporin acts by irreversibly inhibiting an enzyme crucial for the formation of the peptidoglycan layer (i.e. the "cell wall") of the bacteria and the cephalosporins are regarded bactericide (Williams and Lemke 2002). Cephalosporins are mainly used in hospitals.
The drug is excreted unchanged primarily through the kidneys (Tørisen 2007).

Cefuroxime



J01DC02, 55268-75-2
Mw=424.4
pKa=2.59, log D=-3.21

Results from previous screenings
Cefuroxime was not detected in STP influent and STP and hospital effluent water in Norway (Thomas, Langford et al. 2007), and this is the only monitoring conducted in the Nordic countries.

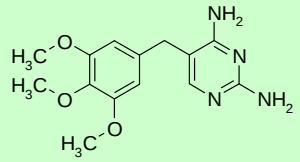
Relevant environmental properties, ERA, and monitoring recommendations
Environmental effects: Toxicity data for the algae *S. capricornutum*, was EC50> 76000 µg/L (72 h) and NOEC ≥ 76000 µg/L (Läkemedelsindustriföreningen 2007), for *Daphnia magna*, EC50> 831000 µg/L (48 h) and NOEC ≥ 831000 µg/L, whereas for a fish (*Oncorhyncus mykiss*), a EC50> 100000 µg/L (96 h) and a NOEL > 100000 µg/L was reported. The PEC/PNEC for **Cefuroxime** is 0.002 (N) and (S). Cefuroxime is not recommended for future monitoring.

Analytical strategy
The preferred method of analysis is SPE (LLE for solid samples) followed by LC-MS.

J01E Sulfonamides and Trimethoprim
Relevant substances: mode of action and pharmacokinetics
Trimethoprim (J01EA01) and **Sulfamethoxazole** (J01EE01) are often administered together in a 1 to 5 ratio. **Trimethoprim** inhibits dihydrofolate reductase (yielding tetrahydrofolate), an enzyme important in the endogenous synthesis of DNA bases in bacteria (but also in eukaryotes) (Williams and Lemke 2002). **Sulfamethoxazole** inhibits a different step in the synthesis of tetrahydrofolate. It is believed that the bacteria will not be able to cope with the combination of **Sulfamethoxazole** and **Trimethoprim** in developing resistance (Williams and Lemke 2002). **Trimethoprim** is excreted (50%) unchanged through urine and **Sulfamethoxazole** is partly degraded by N_4-acetylation and glucuronidation (Williams and Lemke 2002).

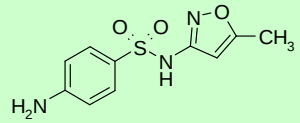
Results from previous screenings
In Norway, both compounds have been detected at STPs (Møskeland 2006; Thomas, Langford et al. 2007), but also in Sweden (Bendz, Paxeus et al. 2005), hospital effluent (Thomas, Langford et al. 2007), in sludge (Møskeland 2006; Thomas, Langford et al. 2007), and in recipient sediment (Møskeland 2006). **Sulfamethoxazole** and **Trimethoprim** have occasionally been detected at concentrations in the same range or above PNEC.

Trimetoprim



J01E A01, J01E E01, 738-70-5
$C_{14}H_{18}N_4O_3$, Mw=290.3
pKa=7.2, log D=0.38

Sulfamethoxazol



J01E E01, 723-46-6
$C_{10}H_{11}N_3O_3S$, Mw=253.2815
pKa=5.81, log P/D=-0.27

Relevant environmental properties, ERA, and monitoring recommendations
Trimethoprim exhibits some toxicity towards the red algae *Rhodomonas salina* and **Sulfamethoxazole** towards a blue green algae (Cyanobacteria) *Microcystis aeruginosa* (Läkemedelsindustriföreningen 2007). Furthermore, **Trimethoprim** is causing concern as it is relatively persistent (Khetan and Collins 2007). **Sulfamethoxazole** (CAS 723-46-6) and **Trimethoprim** (see Veterinary pharmaceuticals selection for environmental monitoring, below) with PEC/PNEC 1.96 (N) and 6.58 (S), and 0.03 (N) and 0.01 (S), respectively should be prioritised for future screening. The annual consumption of these substances was approximately 1.2 and 0.7 tonnes in Sweden 2006, respectively. Trimethoprim use in Norway is slightly higher at ca. 1.4 tonnes.
Sulfamethoxazole seems to be very persistent according to test data displayed at fass.se where 0% degradation was observed after 28 d (OECD 301D and OECD 302B).

Analytical strategy
SPE combined with LC-MS should be used to detect these substances.

J01F Macrolides, Lincosamides, and Streptogramins
Relevant substances: mode of action and pharmacokinetics
Lincosamide antibiotics come from the actinomyces *Streptomyces lincolnensis* and are used to treat susceptible anaerobic bacteria. The consumption in 2006 of the substance was approximately 0.5 tonnes in Norway and 1.7 tonnes in Sweden. **Clindamycin** is also used as a veterinary pharmaceutical**.**

Results from previous screenings
Clindamycin has not yet been part of Nordic screening studies.

Relevant environmental properties, ERA, and monitoring recommendations
The compound chosen for monitoring in Norway and Sweden from this group is **Clindamycin** due to an estimated PEC/PNEC of 0.04 (N) or 0.072 (S).

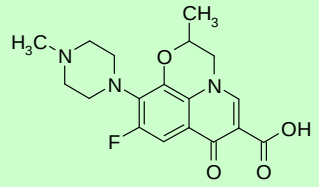
Analytical strategy
SPE combined with LC-MS should be used to detect these substances.

J01M Quinolone Antibacterials
Relevant substances: mode of action and pharmacokinetics
The quinolones are a family of broad-spectrum antibiotics. The parent of the group is nalidixic acid. The majority of quinolones in clinical use belong to the subset of fluoroquinolones, which have a fluor group attached the central ring system, typically at the 6-position. Quinolones and fluoroquinolones are bactericidal drugs, actively killing bacteria. Quinolones inhibit the bacterial DNA gyrase and topoisomerase IV enzymes, thereby inhibiting DNA replication and transcription(Williams and Lemke 2002). **Ofloxacin** (J01M A01), **Ciprofloxacin** (J01M A02), and **Norfloxacin** (J01MA06) are second-generation quinolones (Williams and Lemke 2002). They are excreted unchanged (95-100%) through the kidneys (Tørisen 2007). **Norfloxacin** is not in use in Norway as per November 2007.

Results from previous screenings
Ofloxacin was detected in STP influent water, but not in STP effluent and recipient surface water in Finland (Vieno, Tuhkanen et al. 2006).
Ciprofloxacin was detected in STPs in both Finland and Norway (Møskeland 2006; Vieno, Tuhkanen et al. 2006; Thomas, Langford et al. 2007), and also in recipient surface water and even in drinking water in Finland (Vieno, Tuhkanen et al. 2006). In Norway, **Ciprofloxacin** has been detected also in hospital effluent water, sludge, leachate, and sediment (Møskeland 2006; Thomas, Langford et al. 2007). The

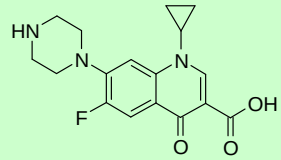
measured concentrations are in the same range or above PNEC.
Norfloxacin was not detected in STPs and surface water in Finland (Vieno, Tuhkanen et al. 2006).
Ofloxacin and **Ciprofloxacin** have occasionally been detected at concentrations in the same range or above PNEC.

Ofloxacin



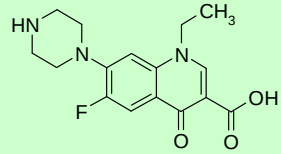
J01M A01, 82419-36-1
$C_{18}H_{20}FN_3O_4$, Mw=361.4
pKa=5.97 (COOH), 7.65 (=NH_2^+), log D= 0.39

Ciprofloxacin



J01M A02, S01A X13, S02A A15,85721-33-1
$C_{17}H_{18}FN_3O_3$, Mw=331.4,
pKa=6.27 (COOH), 8.87 (=NH_2^+), log D= 0.28

Norfloxacin



J01MA06, 70458-96-7
$C_{16}H_{18}FN_3O_3$, Mw=319.3
pKa=6.26 (COOH), 8.85 (=NH_2^+), log D=1.03

Relevant environmental properties, ERA, and monitoring recommendations
An experimentally derived Koc of 61,000 indicates that **Ciprofloxacin** is expected to adsorb to suspended solids and sediment (NIH 2007) and an estimated BCF of 3.2 suggests the potential for bioconcentration in aquatic organisms is low. Quinolone antibacterials are generally phototoxic with potential DNA damage as the most concerning effect. The drug chosen for monitoring in Norway and Sweden from this group is **Ciprofloxacin.** In 2006, the annual human consumption of the substance was approximately 1 tonne in Norway and 2.1 tonnes in Sweden. A recent study in Norway showed that **Ciprofloxacin** MECs may exceed its PNECs (N: 55.38, S: 0.61) suggesting that this compound may pose a risk to the aquatic environment (Thomas et al., 2007). **Ciprofloxacin** also readily partitioned onto sludge with high concentrations being measured in WTP final sludge, which may end up being disposed of on land (Thomas et al., 2007).
Enrofloxacin, a veterinary pharmaceutical, is partly metabolised to **Ciprofloxacin**, and may contribute to additional release of the latter. Fluoroquinolones are known to be very persistent in the environment (Halling-Sørensen, et al., 2007.). It is quite rational that antibiotics with high specificity are prone to be slowly biodegradable by microorganisms. An extensive study by Lindberg et al., points out that **Ciprofloxacin** is largely being distributed from the water phase to the sludge- or sediment phase in the STP. Mass balance calculations indicated that up to 70% ends up in the sludge upon passage of a Swedish STP. Doctors use the fluoroquinolone class of antibiotics to treat food poisoning caused by *Campylobacter*. But after poultry farmers began using fluoroquinolones to treat respiratory disease in flocks, the drugs became less effective in people. In 2005, the FDA banned the use of fluoroquinolones on poultry farms because of these concerns.

Analytical strategy
Quinolone antibacterials are isolated from aqueous matrices by SPE and from solid matrices by liquid extraction, followed by LC-MS.

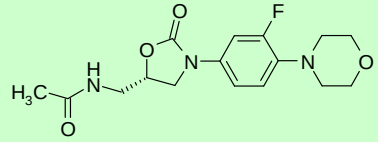
J01X Other Antibacterials
Relevant substances: mode of action and pharmacokinetics
Linezolid (J01X X08) probably works by preventing the formation of the ternary complex between N-formylmethionyl-tRNA ($tRNA^{f\text{-}Met}$)-mRNA-70S subunit, important for protein synthesis (Williams and Lemke 2002). **Linezolid** undergoes non-enzymatic oxidation and renal excretion (30% unchanged) (Tørisen 2007).

Results from previous screenings
Linezolid is only detected in Halden, Norway, (STPs, sediment, and sludge) where it is produced (Møskeland 2006).

Relevant environmental properties, ERA, and monitoring recommendations
Data is missing regarding environmental effects (Läkemedelsindustriföreningen 2007).

Analytical strategy
SPE or LLE was used prior to LC-MS analysis.

Linezolid



J01X X08, 165800-03-3
$C_{16}H_{20}FN_3O_4$, Mw=337,4
pKa=5.75, log P/D=0.41

5.2.8. L Antineoplastic and immunomodulating agents

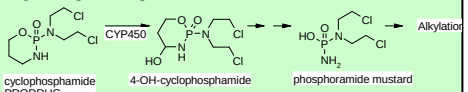
This highly toxic class of drugs is primarily used in hospitals, where they are important in cancer treatment.

L01A Alkylating Agents
Relevant substances: mode of action and pharmacokinetics
The mechanism of action of **Cyclophosphamide** (L01A A01) and **Ifosfamide** (L01A A06) acts through the formation of a cross link between to guanine bases of opposite strands in DNA. Once alkylated, the DNA become prone to cleavage at the alkylated site resulting in formation of single strand breaks of nuclear DNA. Both drugs require CYP mediated metabolism to become active. Less than 20% of both is excreted unchanged in the urine (Tørisen 2007).

Results from previous screenings
Cyclophosphamide was not detected in hospital effluent water, STPs and sludge in a Norwegian study, but **Ifosfamide** was detected in both hospital and STP effluent water in the same study (Thomas, Langford et al. 2007).

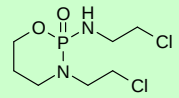
Relevant environmental properties, ERA, and monitoring recommendations
The log Kow of 0.63 indicates that **Cyclophosphamide** is not expected to adsorb to suspended solids and sediment. Neutral hydrolysis calculated half-life for **Cyclophosphamide** at 25°C is 41 days. According to an estimated BCF of 3, the potential for bioconcentration in aquatic organisms is low (NIH 2007). The environmental effects are largely unknown (Läkemedelsindustriföreningen 2007; NIH 2007), but these compounds are designed to be cytotoxic. On the other hand, little of these componds will be released into the sewage, if used properly. **Cyclophosphamide** and **Ifosfamide** have previously been identified as compounds "probably" attributed to genotoxicity found in effluent waste waters in Germany (Steger-Hartmann, Kummerer et al. 1996). **Ifosfamide** should be included in future monitoring programs for hospital effluents.

Cyclophosphamide



L01A A01, 50-18-0
$C_7H_{15}Cl_2N_2O_2P$, Mw=261.1
pKa=2.84, log D=0.23

Ifosfamide



L01A A06, 3778-73-2
$C_7H_{15}Cl_2N_2O_2P$, Mw=261.1
pKa=1.45, log D= 0.39

Analytical strategy
To monitor these compounds, SPE combined with LC-MS should be used.

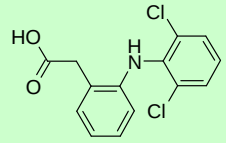
5.2.9. M Musculo-skeletal system

M01 Anti-inflammatory and Anti-rheumatic Products

Relevant substances:mode of action and pharmacokinetics
Diclofenac (M01A B05), **Ibuprofen** (M01A E01), **Naproxen** (M01A E02), and **Ketoprofen** (M01A E03) inhibit the enzyme cyclooxygenase (COX) that synthesise prostaglandins. Prostaglandins are involved in fever, pain and inflammation generation. **Diclofenac**, **Ibuprofen** (ranked 18th by DDD turn over in 2006), **Naproxen** and **Ketoprofen** belong to the Non Steroidal Anti-Inflammatory Drugs or Agents (NSAID/NSAIA).
Results from previous screenings
Diclofenac has been identified in STPs in Norway, Sweden and Finland, hospital effluent, recipient water, leachate, sediment,

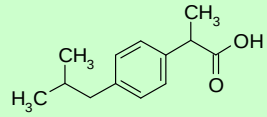
and sludge.(Weigel, Berger et al. 2004; Lindqvist, Tuhkanen et al. 2005; Andersson, Woldegiorgis et al. 2006; Thomas, Langford et al. 2007).
Five reports exist on the monitoring of **Ibuprofen** in the Nordic environment (Weigel, Berger et al. 2004; Lindqvist, Tuhkanen et al. 2005; Andersson, Woldegiorgis et al. 2006; Møskeland 2006; Thomas, Langford et al. 2007). Matrices from which **Ibuprofen** has been detected include leachate, STPs, hospital effluent, sludge, recipient water, manure from animal keeping, surface and sea water, and sediment, but not biota. Weigel et al. also included and detected the Ibuprofen metabolites **Ibu-OH** and **Ibu-COOH** (Weigel, Berger et al. 2004).

Diclofenac



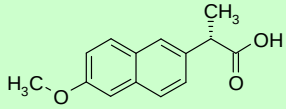
M01A B05, 15307-86-5
$C_{14}H_{11}C_{l2}NO_2$, Mw=296.2,
pKa=4.15, log D= 1.28

Ibuprofen



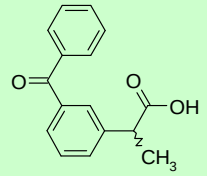
M01A E01, 15687-27-1
$C_{13}H_{18}O_2$, Mw=206.3,
pKa=4.91, log D=1.16

Naproxen



M01A E02, 22204-53-1
$C_{14}H_{14}O_3$, Mw=230.3
pKa=4.15, log D=0.85

Ketoprofen



M01A E03, 22071-15-4
$C_{16}H_{14}O_3$, Mw=254.3
pKa=4.45, log D=0.09

Ketoprofen and **Naproxen** has been detected in STPs in Finland and Sweden (Lindqvist, Tuhkanen et al. 2005; Andersson, Woldegiorgis et al. 2006), and in leachate, hospital effluent, sludge, recipient water, manure from animal keeping, surface water and sediment in Sweden (Andersson, Woldegiorgis et al. 2006). **Diclofenac, Naproxen, and Ibuprofen** has been detected at concentrations in the same range or above PNEC.

Relevant environmental properties, ERA, and monitoring recommendations
The NSAID-group consists of a number of predominantly acidic drugs. **Ibuprofen** and **Naproxen** are considered to result in insignificant environmental risk (Läkemedelsindustriföreningen 2007). Available ecotoxicological data does exclude **Ketoprofen** from possessing an environmental risk (Läkemedelsindustriföreningen 2007). The substances are sold in wide variety of formulations yielding a very high estimated environmental release (e.g. total consumption of **Ibuprofen**, **Ketoprofen**, **Naproxen** and **Diclofenac** add up to approximately 90 tonnes in Sweden 2006). Despite being degraded slowly in the environment, the use of **Diclofenac** is considered to result in insignificant environmental risk (Läkemedelsindustriföreningen 2007). However, this view is strongly opposed by findings in India where vulture abundance was diminished by 90% due to a proposed diclofenac bioaccumulation (Oaks, Gilbert et al. 2004). Recent (non-standardised) eco-toxicological studies indicate that **Diclofenac** induces haematological changes such as a decrease of the haemoglobin content. Pathological alterations included renal, hepatic, intestinal as well as gill lesions. Furthermore, **Diclofenac** has been shown to accumulate in various tissues of fish (Schwaiger et al., 2004).

Diclofenac is not considered readily biodegrade according to fass.se ("55.5 % in 28 days, 19 - 21 °C, OECD 301D"). Due to a rather high log Kow (4.5) the substance possesses the potential to bioaccumulate. Another finding from previous monitoring studies in Sweden further augmenting for **Diclofenac** on the list is that analysis of aqueous samples from STPs are puzzling. Often effluent concentrations of **Diclofenac** are higher than the corresponding influent concentrations from the same STP. This is probably due to de-conjugation of the

drug in the STP-process, see Figure 1 (Andersson et al., 2006).

Also, in a Swedish study, the fish plasma concentrations of **Ibuprofen**, **Diclofenac**, **Ketoprofen**, and **Naproxen** were higher than predicted by the "Fish Plasma Model (Brown, Paxeus et al. 2007). The individual drug chosen for monitoring in Sweden from this group is **Diclofenac**. The annual consumption of the substance was approximately 4 tonnes in Sweden 2006. For Norway it is recommended that in addition to **Diclofenac** (PEC/PNEC; N: 4.31, S: 5.99), **Ibuprofen** (N: 1.29, S: 1.57) and **Naproxen** (N: 1.74, S: 2.71) are also included in future monitoring programmes, the latter two are included due to their high load.

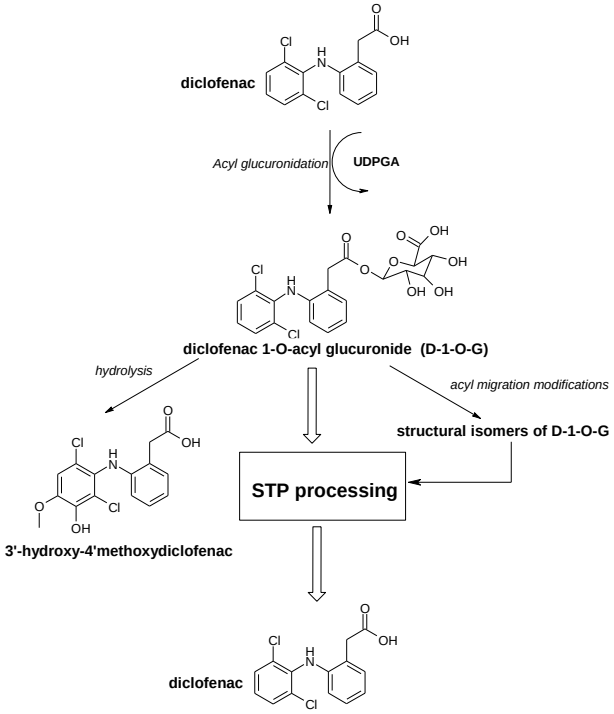


Figure 1: Likely de-conjugation route of Diclofenac in the STP-process.

Analytical strategy
Following SPE (water samples) or LLE (solid samples), both GC-MS and LC-MS has been employed. GC-MS requires derivatisation of the drugs prior to analysis.

M04 Antigout preparations
Relevant substances: mode of action and pharmacokinetics
Allopurinol is a drug used primarily to treat conditions arising from excess uric acid, most notably chronic gout with an annual consumption rate of approximately 2 tonnes in Norway (2006).

Results from previous screenings
Allopurinol has not yet been part of Nordic screening studies.

Relevant environmental properties, ERA, and monitoring recommendations
Allopurinol with a PCE/PNEC of 1.18 (N) and 1.26 (S) should be included in future screening activities.

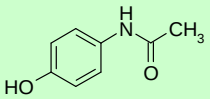
Analytical strategy
Following SPE (water samples) or LLE (solid samples), LC-MS can be employed for analysis.

5.2.10. N Nervous system

N02 Analgetics
Relevant substances: mode of action and pharmacokinetics
Paracetamol (N02B E01) has the same mode of action as the M01 drugs. However, **Paracetamol** has only weak anti inflammatory activity and is therefore not regarded as an NSAID. It is commonly used, and except for **Sodium Fluoride**, it is the most used non

prescription drug in Norway (ranked 9th by DDD in 2006). It is metabolised in the liver to sulfonate and glucuronide conjugates (Tørisen 2007).

Paracetamol



N02B E01, 103-90-2
$C_8H_9NO_2$, Mw=151.2
pKa=9.54, log D=0.34

Results from previous screenings
Paracetamol has been detected in Norwegian hospital effluent water and STP, but not in sludge (Thomas, Langford et al. 2007). **Paracetamol** was detected at concentrations in the same range or above PNEC.

Relevant environmental properties, ERA, and monitoring recommendations

Paracetamol is slowly degraded in aqueous environment, but does not bioaccumulate (Läkemedelsindustriföreningen 2007). A log Kow of 0.46 indicates that **Paracetamol** is not expected to adsorb to suspended solids and sediment. The LC_{50} for *Pimephales promelas* (Fathead minnow) is 814 mg/L over 96 hr (NIH 2007). This group of drugs is one of the major contributors to environmental release of pharmaceuticals worldwide. The drug chosen for monitoring in Sweden and Norway from this group is **Paracetamol**. The annual consumption (2006) of the substance was approximately 170 tonnes in Norway and 411 tonnes in Sweden. **Paracetamol** (PEC/PNEC N: 5.52, S: 6.70) is not considered very toxic with a PNEC of 9.2 µg/L and is efficiently eliminated during sewage treatment processes (Roberts and Thomas, 2006; Thomas et al., 2007). However, the amount of **Paracetamol** sold in both Norway and Sweden exceeds most pesticides and herbicides used in Swedish agriculture and it needs continuous environmental monitoring.

Analytical strategy

Following SPE (water samples) or LLE (solid samples), both GC-MS and LC-MS has been employed. GC-MS requires derivatisation of the drugs prior to analysis.

N03 Anti-epileptics

Relevant substances: mode of action and pharmacokinetics

This group of drugs are used as anticonvulsant and mood stabilizing drugs, used primarily in the treatment of epilepsy and bipolar disorder. **Carbamazepine** (N03A F01) acts on voltage dependent sodium channels to prevent the spread of seizures. **Carbamazepine** depresses synaptic transmission in the reticular activating system, thalamus, and limbic structures (Williams and Lemke 2002). 3% of **Carbamazepine** is excreted unchanged (Khetan and Collins 2007), but its metabolite **carbamazepine-10,11-epoxide** is active, while the environmental properties are largely unknown. At a daily dosage of 1200 mg, this means that a single patient excretes at least 36 mg of **Carbamazepine** into the environment every day.

Results from previous screenings

Carbamazepine has been detected in STP influent, but not STP effluent water or sea water in Norway (Weigel, Berger et al. 2004), whereas in Finland it was detected in STP in- and effluent water as well as in recipient river water (Vieno, Tuhkanen et al. 2006).

Relevant environmental properties, ERA, and monitoring recommendations

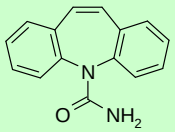
Carbamazepine is prevalent due to poor STP removal (Daughton and Ternes 1999), with a 50% dissipation time of 82±11 days (Khetan and Collins 2007). However, the environmental effects of the presence of **Carbamazepine** remains unclear. Eve Dussault, a graduate student at Guelph University (Canada), presented data on **Carbamazepine** at a Society of Environmental Toxicology and Chemistry meeting in November and estimated the environmental half-life to be at least 80 days. The substance must thus be regarded as potentially persistent. Photolysis studies on **Carbamazepine** indicate a very complex degradation pattern including formation of the very toxic compound acridine (Chiron et al., 2006). **Carbamazepine** (CAS 298-46-4) yielded a PEC/PNEC of 0.21 (N) and 0.22 (S) and is recommended for future monitoring.

Analytical strategy

For aqueous samples, SPE followed by LC-MS is recommended.

N05 Psycholeptics
N05B Anxiolytics
Benzodiazepines

Carbamazepine



N03A F01, 298-46-4
Mw=236.3
pKa=13.9, log P=2.45

Relevant substances: mode of action and pharmacokinetics

The benzodiazepines are a class of psychoactive drugs considered minor tranquillisers with varying hypnotic, sedative, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties, which are mediated by slowing down

the central nervous system. Its mode of action is to inhibit a chloride channel within the CNS.

Results from previous screenings
Oxazepam was frequently detected in aqueous samples in a previous monitoring programme in Sweden (Woldegiorgis et al. 2007).

Relevant environmental properties, ERA, and monitoring recommendations
The drug chosen for monitoring in Norway and Sweden from this group is **Oxazepam** (CAS 604-75-1). The annual consumption of the substance was approximately 0.6 tonnes in both Norway and Sweden 2006. When **Oxazepam** was introduced on the market in 1985 in UK, ERA was not a regulatory demand from authorities, thus very little environmentally relevant data on for instance ecotoxicity can be found. When establishing a monitoring programme for the benzodiazepines it is very important to consider the metabolic fate of these substances. For instance, **Diazepam**, also on the PEC/PNEC-list, is being converted to **Oxazepam** prior to excretion (Figure 2).

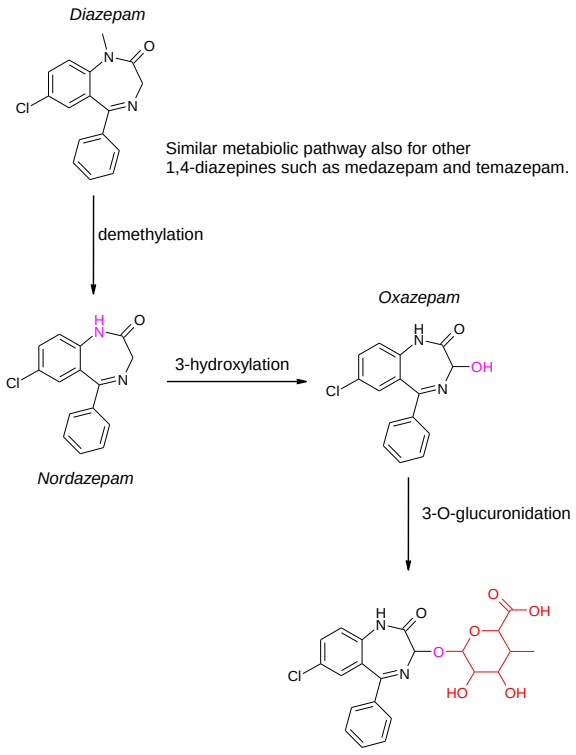


Figure 2: Metabolic pathway for diazepam and Oxazepam

Zopiclone

N05C F01, 43200-80-2
$C_{17}H_{17}ClN_6O_3$, Mw=388.8
pKa=6.79, log D=0.53

Analytical strategy
For aqueous samples, SPE followed by LC-MS is recommended.

N05C Hypnotics and Sedatives
Relevant substances: mode of action and pharmacokinetics
Zopiclone (N05C F01) is a short acting hypnotic that binds to the $GABA_A$ receptor (a chloride ion channel) in the central nervous system (CNS). The reason why this induces sleep is unclear (Williams and Lemke 2002). Based on DDD, **Zopiclone** ranked 7th in turn over (2006). **Zopiclone** is metabolised in the liver by CYP 3A4 and CYP 2C8 to two major metabolites without clinical significance, and 5% is excreted unchanged in urine (Läkemedelsindustriföreningen 2007). The non-benzodiazepines are comparatively new drugs whose actions are very similar to those of the benzodiazepines, but are structurally unrelated to the benzodiazepines and are believed to have fewer side effects. The "Z-drugs" **Zolpidem** (N05CF02) and **Zopiclone** (N05CF01) are both strong sedatives used exclusively for the treatment of insomnia.

Results from previous screenings
In a Norwegian study, **Zopiclone** has been detected in STP influent and effluent water and in sludge as well as in river sediment in close proximity of the STP (Møskeland 2006). **Zolpidem** has not been screened in the Nordic environment.

Relevant environmental properties, ERA, and monitoring recommendations
The environmental effects of **Zopiclone** are not known (Läkemedelsindustriföreningen 2007; NIH 2007). No PEC/PNEC has been calculated. The compound chosen for monitoring is **Zolpidem** (CAS 82626-48-0). The an-

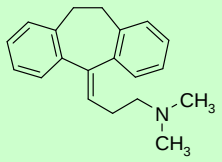
nual consumption of the substance was approximately 4.3 tonnes in Sweden 2006. However, only 60 kg was used in Norway and therefore the risk quotient is much lower at present ($PEC/PNEC_{ECOSAR}$; N: 0.03, S: 1.23). **Zolpidem** has previously been identified by the medical committee of the Stockholm City County Council as an "environmentally problematic" substance and advised medical practitioners working in the county to reduce the prescription of **Zolpidem**. Should sales of **Zolpidem** in Norway increase and if occurrence is reported in Sweden then the compound should be considered for inclusion also in Norway.

Analytical strategy
SPE combined with LC-MS is the preferred method to analyse **Zolpidem**.

N 06 Psychoanaleptic Drugs
N06AA. Non-Selective Monoamine Reuptake Inhibitors
Relevant substances: mode of action and pharmacokinetics
The monoamine theory states that depression is caused by a functional deficit of monoamine transmitters at certain sites in the brain (Rang, Dale et al. 1999). The tri-cyclic antidepressants (TCA) **Amitriptyline** (N06A A09), **Clomipramine** (N06A A04), **Nortriptyline** (N06A A10), and **Doxepin** (N06A A12) act by inhibiting reuptake of the neurotransmitters noradrenalin and serotonin from synapses in CNS. The TCAs are typically N-demethylated and the metabolites biologically active.

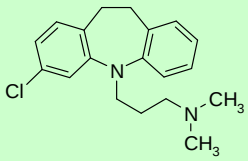
Results from previous screenings
There is only one report on these compounds, all determined in STP effluent water. Ho et al. (Ho, Vasskog et al. 2007) filtered 1.1 L water and used adjusted it to pH~11. Liquid phase micro extraction (LPME) with dihexyl ether separating the donor and the 10 mM HCOOH acceptor solution (20 µL) was utilised for the extraction. The micro extracts were then analysed by LC-ESI-MS/MS. Only one sample was analysed (in triplicate) and the concentrations reported were as follows: **Amitriptyline** 12.9 ng/L (mLOQ 25 pg/L), **Nortriptyline** 2.7 ng/L (mLOD 6 pg/L), **Clomipramine** was detected at a concentration between mLOD (18 pg/L) and mLOQ (53 pg/L) and **Doxepin** was present at a concentration similar to mLOD (11 pg/L). In the work of Ho et al. a 25,000-fold pre-concentration was obtained, and three phase based LPME systems represent a very attractive technique for ionisable PPCP. However, precautions must be taken for alkaline or acid labile compounds. Furthermore, LPME requires skilled operators and reasonable to poor precision is obtained.

Amitriptyline



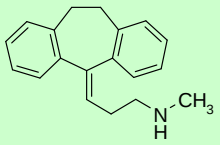
N06A A09, 50-48-6
$C_{20}H_{23}N$, Mw=277.4
pKa=9.4, log P= 4.9

Clomipramine



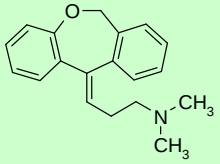
N06A A04, 303-49-1
$C_{19}H_{23}ClN_2$, Mw=314.9
pKa=9.4, log P= 5.2

Nortriptyline



N06A A10, 72-69-5
$C_{19}H_{21}N$, Mw=263.4
pKa=9.7, log D= 1.7

Doxepine



N06A A12, 1668-19-5
$C_{19}H_{21}NO$, Mw=279.4
pKa=9.19, log D=1.72

Relevant environmental properties, ERA, and monitoring recommendations
Environmental effects of TCAs cannot be excluded as data are missing. The compounds degrade slowly in aqueous environments and they presumably bioaccumulate (Läkemedelsindustriföreningen 2007). An estimated BCF of 1,226 was calculated for **Amitriptyline**, based on a log Kow of 4.92, suggesting the potential for bioconcentration in aquatic

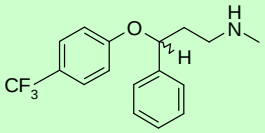
organisms is very high (NIH 2007). An LC50 of 0,081 mg/L is reported for *Brachionus calyciflorus*. **Clomipramine**, **Nortriptyline**, and **Doxepin** are chemically closely related to **Amitriptyline**, suggesting similar properties for all these compounds. PEC/PNEC is calculated for **Amitriptyline**; 1.05 (N) and 1.04 (S). **Amitriptyline** was detected at concentrations in the same range or above PNEC. It is proposed that **Amitriptyline** warrants further screening in Norway. Amitriptyline has annual consumption rate of nearly 0.3 tonnes in Norway.

Analytical strategy
SPE or LPME combined with LC-MS. The amounts used are rather small and to successfully detect these substances, a high preconcentration must be obtained, which is obtained by utilising LPME.

N 06 AB. Selective serotonin reuptake inhibitors
Relevant substances: mode of action and pharmacokinetics
The selective serotonin reuptake inhibitors (SSRI) **Fluoxetine** (N06AB03), **Citalopram** (N06AB04), **Paroxetine** (N06AB05), **Sertraline** (N06AB06), and **Fluvoxamine** (N06AB08) work by (contrary to the TCA) by selectively inhibit the reuptake of serotonin from synaptic gaps in CNS. Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants used in the treatment of depression, anxiety disorders, and some personality disorders. SSRIs are extensively metabolised by CYP450 yielding both active and inactive metabolites.

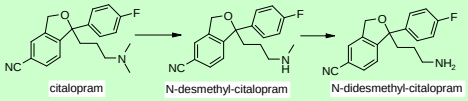
Results from previous screenings
Weigel et al. (Weigel, Berger et al. 2004) did not detect **Fluoxetine** in STP influent and effluent. Sample preparation was conducted by filtration and pH~7 prior to SPE (Oasis), followed by LC-ESI-MS/MS. The mLOD was not reported. By the same method, **Paroxetine** (0.02 µg/L) and **Sertraline** (0.1 µg/L) were detected in STP influent, but not effluent water.
A further development of the SPE method was conducted by Vasskog et al. (Vasskog, Berger et al. 2006), who implemented two subsequent LLE steps hence obtaining cleaner extracts. LC-ESI-MS/MS was used for compound identification. The following concentrations were reported in influent (i) and effluent (e) psychiatric hospital STP water: **Citalopram** (mLOQ 0.16 ng/L); 13-680 (i) and 9.2-382 ng/L (e), **Fluoxetine** (mLOQ 0.12 ng/L); 0.4-2.4 (i) and 1.2-2.3 ng/L (e), **Fluvoxamine** (mLOQ 0.15 ng/L); 0.4-3.9 (i) and <mLOQ-0.4 ng/L (e), **Paroxetine** (mLOQ 0.12 ng/L); 0.5-1.6 (i) and 0.6-12.3 ng/L (e), **Sertraline** (mLOQ 0.29 ng/L); 1.8-16.3 (i) and 0.9-2.0 ng/L (e). **Fluoxetine** and **Sertraline** were detected at concentrations in the same range or above the PNEC estimated in the present study.

Fluoxetine



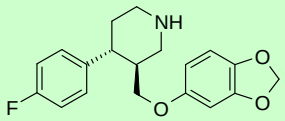
N06A B03, 54910-89-3
$C_{17}H_{18}F_3NO$, Mw=309.3
pKa=10.05, log D=1.31

Citalopram



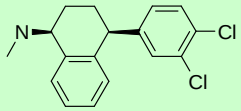
N06A B04, 59729-33-8
$C_{20}H_{21}FN_2O$, Mw=324.2
pKa=9.59, log D=0.06

Paroxetine



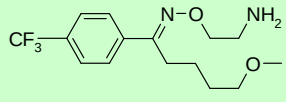
N06A B05, 61869-08-7
$C_{19}H_{20}FNO_3$, Mw=329.4
pKa=10.32, log D=1.0

Sertraline



N06A A12, 79617-96-2
$C_{16}H_{16}Cl_2N$ Mw=293.2
pKa=9.47, log P/D=2.43

Fluvoksamin



N06A B08, 54739-18-3
$C_{15}H_{21}F_3N_2O_2$, Mw=318.3
pKa=9.39, log D=0.8

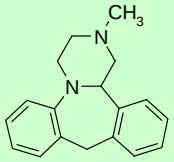
In another Norwegian study, **Fluoxetine** was only detected in sludge of all the different matrices investigated (leachate, STP, recipient surface water and sediment) (Møskeland 2006) SSRIs are extensively metabolised, but these are not included in the abovementioned reports. However, recently a report by Vasskog and co-workers has been submitted where SSRIs and their metabolites are monitored in environmental samples [Vasskog, personal communication].

Relevant environmental properties, ERA, and monitoring recommendations
Over the last decade the consumption of SSRI drugs has increased rather rapidly in Sweden (total consumption in 1995 ~1 tonne, total consumption in 2006 >5 tonnes). The drugs chosen for monitoring in both Norway and Sweden from this group are **Fluoxetine** and **Sertraline**. The annual consumption of these substances was approximately 0.3 and 2.5 tonnes in Sweden 2006, respectively, with much lower volumes being consumed in Norway. **Fluoxetine** is moderately toxic (both acute and chronic) towards most algae and crustaceans, and very toxic to mussels while **Sertraline** is toxic towards algae and crustaceans in particular. None of the SSRI drugs has a pronounced potential to bioaccumulate (rather low log Kow-values) but **Sertraline** has although a strong propensity to re-distribute from the aqueous phase to the sediment- or sludge phase (in STPs). **Sertraline** is regarded as slowly degraded in the environment according to fass.se. 9-32% of **Sertraline** was left after 45 days using an active sludge test. A $t_{½}$ of 4.6 d was determined in an indirect photolysis experiment. Monitoring data suggests that **Sertraline** should preferentially be monitored in sludge or sediment samples (Woldegiorgis et al. 2007). Fong demonstrated that SSRIs induced spawning in the zebra mussel *Dreissena polymorpha* (a non-target organism for SSRI) at sub μM concentrations (Fong 1998). The SSRIs is a class of compound causing environmental concern, as reflected by their PEC/PNEC: **Fluoxetine** 4.437 (N) and 11.092 (S), **Sertraline** 3.037 (N) and 6.580 (S), **Paroxetine** 0.028 (N) and 0.024 (S), **Citalopram** 0.018 (N) and 0.051 (S). **Fluoxetine, Citalopram** and **Sertraline** are recommended for further monitoring. Citalopram has an annual consumption rate of nearly 0.3 tonnes in Norway and has recently been detected at high concentrations in sludge collected from both Swedish and Norwegian STPs (Barron, Unpublished data).

Analytical strategy
SPE or LPME combined with LC-MS. The amounts used are rather small and to successfully detect these substances, a high preconcentration must be obtained, which is obtained by utilising LPME. At NILU, LPME is presently tested and evaluated in collaboration with University of Tromsø.

N06AX Other Antidepressants
Relevant substances: mode of action and pharmacokinetics
The mechanism of **Mianserine** (N06A X03) is unknown, as it does not affect amine reuptake (Rang, Dale et al. 1999). **Mianserine** is extensively metabolised by N-demethylation and (ring) oxidation, followed by conjugation (Tørisen 2007).

Mianserine



N06AX03, 24219-97-4
$C_{18}H_{20}N_2$, Mw=264.4
pKa= 8.3, log P= 3.8

Results from previous screenings
Mianserine has been detected in STP effluent water in Norway (Ho, Vasskog et al. 2007).

Relevant environmental properties, ERA, and monitoring recommendations
Mianserine is not regarded as an environmentally high risk compound, but it is relatively persistent and may bioaccumulate (Läkemedelsindustriföreningen 2007). **Mianserine** is not recommended for further monitoring.

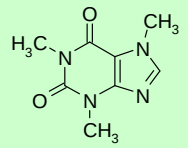
Analytical strategy
LPME followed by LC-MS was used in the analyses.

N06B Psychostimulants, Agents Used for ADHD and Nootropics
Relevant substances: mode of action and pharmacokinetics
The major source of **Caffeine** (N06BC01) in

the environment is from tea and coffee, not from administered drugs. There are few clinical uses for **Caffeine**, but it is found in combination praparations for treating head ache (e.g. **Phenazon-Caffeine**).
It is converted in the liver to its mono-, di-, and tri-demethylated metabolites (Williams and Lemke 2002).

Results from previous screenings
Caffeine has been detected in sea water and STP effluent in a Norwegian investigation (Weigel, Berger et al. 2004).

Caffeine



N06B C01, 58-08-2
$C_8H_{10}N_4O_2$, Mw=194.2,
pKa=>14.0, log P/D=-0.13

Relevant environmental properties, ERA, and monitoring recommendations
The environmental effects of caffeine are uncertain. A log Kow of -0.07 indicates that **caffeine** is not expected to adsorb to suspended solids and sediment. PEC/PNEC is not calculated. It is not necessary to monitor caffeine in the future, but it could be implemented to confirm dispersion.

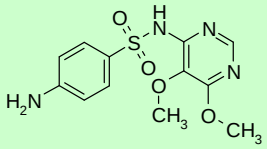
Analytical strategy
SPE followed by GC-MS is the preferred method for aqueous samples.

5.2.11. P Anti-parasitic products, insecticides and repellents

Relevant substances: mode of action and pharmacokinetics
Sulfadoxine is normally administered along with **Pyrimethamine**, and the combination is called **Fansidar** (P01BD01). **Fansidar** acts by inhibiting two separate steps in the synthesis of tetrahydrofolate in parasites, such as the malign malaria inducing *Plasmodium falciparum* (Williams and Lemke 2002).

Results from previous screenings
Sulfadoxine has been detected in swine manure in Denmark (Jacobsen and Halling-Sørensen 2006).

Sulfadoxine



P01BD01, QJ01E W13, 2447-57-6
$C_{12}H_{14}N_4O_4S$, Mw=310.3
pKa=6.16, log D=-0.55

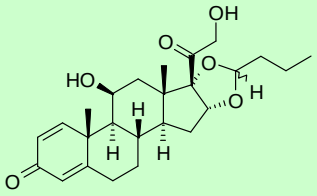
Relevant environmental properties, ERA, and monitoring recommendations
No relevant information was retrieved from fass.se and the estimated PEC/PNEC was far below 0.01. It is not recommended to monitor for **Sulfadoxine** and **Pyrimethamine** in the future.

Analytical strategy
LLE followed by LC-MS was used to analyse **Sulfadoxine** from swine manure.

5.2.12. R Respiratory system

Relevant substances: mode of action and pharmacokinetics
Budesonide (R01A D05) is used to treat lung disease and rhinitis. It is administered locally, and designed to undergo extensive metabolism (Williams and Lemke 2002).

Budesonide



R01A D05, 51333-22-3
$C_{25}H_{34}O_6$, MW=430.54
pKa=n.a., log P=3.14

Results from previous screenings
Despite employing several different matrices, **Budesonide** was not detected in any samples in a Norwegian study (Møskeland 2006), which is attributable to the metabolic pattern of the drug.

Relevant environmental properties, ERA, and monitoring recommendations
Budesonide is known to have adverse effect on *Selenastrum capricornutum* (Läkemedelsindustriföreningen 2007). Furthermore, the compound has a potential for being persistent

and accumulable. However, the PEC/PNEC is low: 0.0002 (N) and 0.0009 (S), and it is not recommended to implement **Budesonide** in future monitoring programs.

Analytical strategy
SPE followed by either LC-MS or derivatisation prior to GC-MS can be used in the analysis of **Budesonide**.

5.2.13. Concluding remarks on the monitoring data of human pharmaceuticals

The selection of compounds in the screening and monitoring reports mentioned in this section seems a little coincidental. Pharmaceuticals targeted for monitoring in the Nordic countries to this date can be divided into the following groups: beta blocking agents, female hormones used for contraception, antibiotics (primarily tetracyclines), NSAID, and antidepressants (i.e. SSRI). Especially beta-blockers, antibiotics and NSAIDs are ubiquitous and have been detected in all Nordic countries in concentrations which are in the same range as or above PNEC.

A few of the compounds reported here, have been monitored despite that they are not expected to be found in the environment in its original form, if the drug has been used appropriately. The effects of metabolites are in most cases not known, but it should be strongly considered to implement metabolites in future monitoring programs. However, from an analytical point of view, metabolites are basically more polar than their parent compounds and represent a challenge in method development. Furthermore, drug metabolites are often difficult to obtain (low commercial availability) and are often terribly expensive. Microsomal synthesis of drug metabolites is one possibility, but this is a tedious process and needs appropriate funding.

5.3. Hospital pharmaceuticals

5.3.1. Contrast media

A specific group of pharmaceuticals not considered in this study but worth mentioning is the contrast medium substances administered to patients in order to enhance X-ray resolution imaging or magnetic resonance imaging. Most of these substances are either iodinated complex organic compounds (the iodine being covalently attached to the organic backbone) or gadolinium complexes of organic salts (the gadolinium being bi-, tri- or pentadentated to the organic counter ion). Contrast media are chemically designed to and non-toxic and extremely persistent within the human. However, these substances are persistent also in the environment. Whether the non-toxicity also applies to aquatic species such as Daphnia and fish is currently not known, as the publicly available ecotoxicological data are scarce and in the case of the gadolinium-based drugs environmentally relevant half-lives ($t_{½}$) have not been found in literature. These compounds will eventually degrade releasing iodine (not particularly harmful) and gadolinium (moderately toxic, EC50 Daphnia <1000 µg/l) to the aquatic environment. It is difficult to calculate the PEC and to assess the environmental risks associated with these drugs as sales data indicate only their costs and not the amounts used. A mitigating factor could be that this group of substances are solemnly administrated to patients when in hospital care, hence unnecessary environmental releases due to incorrect disposal should be minimal. In Sweden (2006) the value of the contrast media drugs sold to the hospitals amounted to 0.25 billion SEK (~25 million €). The amounts of active substances used in contrast media drugs in Europe alone, is estimated to be 100-200 tonnes annually (Dr. R. Laenge, head of ecotox. dept., Bayer Schering Pharma AG, *personal communication*).
In Table 2 the different iodinated or gadolinium-complexed contrast media sold in Sweden are shown along with sales figures and CAS-numbers.

Table 2: Contrast media drugs sold in Sweden including sales figures.

Name	ATC-code	CAS	Sales 2006 (SEK)
Iodinated X-ray contrast media drugs			
Diatrizoic acid	V08AA01	117-96-4	4 782 178
Iohexol	V08AB02	66108-95-0	54 345 149
Ioxaglic acid	V08AB03	59017-64-0	3 351 876
Iopromide	V08AB05	73334-07-3	28 486 446
Ioversol	V08AB07	87771-40-2	28 427 050
Iodixanol	V08AB09	92339-11-2	60 707 055
Iomeprol	V08AB10	78649-41-9	10 063 055
Iobitridol	V08AB11	136949-58-1	8100 777
Gadolinium-complexed contrast media drugs for magnetic resonance imaging			
Gadopentetic acid	V08CA01	80529-93-7	20 835 740
Gadoteric acid	V08CA02	72573-82-1	4 041 173
Gadodiamide	V08CA03	131410-48-5	17 727 160
Mangafodipir (Mn-based)	V08CA05	155319-91-8	209 784
Gadobenic acid	V08CA08	113662-23-0	2 724 018
Gadobutrol	V08CA09	138071-82-6	1 734 776
Gadoxetic acid	V08CA10	135326-11-3	1 415 627
Gadofosveset	V08CA11	-	315 518

These compounds were seldom or never measured in the Nordic environment.

5.3.2. Other pharmaceutical residues from hospitals

Less than 10% of the total consumption of human pharmaceuticals in Sweden occurs in hospitals and 'closed' health facilities (Socialstyrelsen 2001).

However, the drugs administered there are often much more toxic and persistent than the pharmaceuticals in general (toxic to humans and mammalians as in the case of cytostatics) Since the dilution of hospital sewage are very small compared to normal communal sewage (including grey water), the corresponding concentrations are higher (in comparison). Emissions to the hospital sewage are both from hospital toilets as well as from erroneous disposal of residual drugs. Estimates based on an inventory study from a major university hospital in Stockholm in 2000 disclosed that at least 500 litres of liquid pharmaceutical formulations were erroneously being disposed in the hospital sewage annually. The same study indicated however that solid pharmaceuticals being used where predominately being correctly disposed through the cooperation of pharmacies (Liljelund 2000).

The human pharmaceuticals identified as drugs most likely being administered at hospitals are **cytostatic drugs** used in chemotherapy (cancer treatment). In its non-oncological use, the term cytotoxic may also refer to antibiotics (antibacterial chemotherapy). Other uses of cytostatic chemotherapy agents (including the ones mentioned above) are the treatment of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis and the suppression of transplant rejections (immunosuppression and disease-modifying anti-rheumatic drugs (DMARDs) used in many autoimmune disorders). Also some **atypical antipsychotic** drugs may be considered since the predominate use within psychiatric care at hospitals. As previously mentioned, the imaging contrast media are important to consider. Also **radioactive pharmaceuticals** as well as some **anti-viral drugs** needs to be considered when assessing drug primarily being used in the hospitals.

Cytostatic pharmaceuticals
Cytostatic drugs are included in the ATC main group L. The annuals sales volume in Sweden concerning this group is well above €0.43 billion. The majority of chemotherapeutic drugs can be divided into: alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way.

Some newer agents, not considered for environmental monitoring, do not directly interfere with DNA. These include monoclonal antibodies and the new tyrosine kinase inhibitors e.g. **Imatinib mesylate**, which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukaemia, gastrointestinal stromal tumours).

A subgroup of cytostatic drugs (ATC L01XA) also contains the heavy metal Platinum. The annual emissions in Sweden of platinum from medicinal sources have been estimated to be < 5% of the total annual emission (Socialstyrelsen 2001).
Most cytostatic drugs do not have a DDD (from WHO), thus only sales figures will be tabulated in this study. These pharmaceuticals are being administered to the patients in many different forms:
Intravenous injection/infusion, intramuscular and subcutaneous injection, per oral administration, intratecal injection, intravesical instillation, intraperitoneal instillation, intrapericardial instillation, injection in Selker reservoir/Omaya reservoir (on children).
Most of the aforementioned routes require highly skilled medical personnel and generally most Swedish hospitals have together with the regional county councils developed advanced schemes and routines in the handling of cytostatic drugs. For instance there is a "driver's licence" for personnel working with cytostatic treatments including safety and disposal issues.
In Table 3 below a list of the most sold cytostatic drugs having a sales value >1 million SEK in Sweden 2006 are given.

Atypical antipsychotic drugs
From this category the drug **Olanzapine** (CAS 132539-06-1) has been chosen since it is frequently used in psychiatric emergency treatments. The 6.7 million DDDs sold annually in Sweden represents some 70 kg of active substance. There is no information of fate or toxicity of **Olanzapine**.

Anti-viral drugs (hospital treatment)
In particular, two anti-viral pharmaceuticals for treatment of severe influenzas have been identified as predominately used for patients under hospital care. **Amantadine** (CAS 768-94-5, ATC N04BB01) is used in the treatment of elderly persons infected with influence A-strains. The annual sales in Sweden correspond to 3 kg. **Oseltamivir** ("Tamiflu", CAS 196618-13-0, ATC J05AH02) is a potent antiviral drug also prescribed upon indication of human version the bird flu-infections. Annually 8 kg is sold in Sweden. However it is difficult to assess whether all 8 kg are consumed annually since the pharmaceutical have been subjected to hoarding whenever mass media have reported on influenza (flu) epidemics. Whether **Oseltamivir** has problematic environmental properties is largely unknown, fass.se reports a PNEC of 33 µg/L (Water-flea, Daphnia magna, EC50 48 h). Furthermore **Oseltamivir** is not readily biodegradable; however, there is appreciable hydrolysis and an inherent test showed borderline biodegradability (www.fass.se). In the context of antibiotics resistance development, monitoring of **Oseltamivir** may be important.

Table 3: Sales volumes of cytostatics in Sweden.

Name	**CAS**	**ATC**	**Sales volume SEK**
Cyclophosphamide	50-18-0	L01AA01	8 029 955
Melphalan	148-82-3	L01AA03	1 263 639
Ifosfamide	3778-73-2	L01AA06	3 248 145
Temozolomide	85622-93-1	L01AX03	60 972 073
Dacarbazine	4342-03-4	L01AX04	1 674 732
Methotrexate	59-05-2	L01BA01	42 445 280
Pemetrexed	137281-23-3	L01BA04	27 654 391
Mercaptopurine	50-44-2	L01BB02	1 805 150
Cladribine	4291-63-8	L01BB04	1 403 468
Fludarabine	21679-14-1	L01BB05	13 026 835
Cytarabine	147-94-4	L01BC01	13 664 118
Fluorouracil	51-21-8	L01BC02	13 882 386
Gemcitabine	95058-81-4	L01BC05	59 957 041
Capecitabine	154361-50-9	L01BC06	25 904 877
Vinorelbine	71486-22-1	L01CA04	19 022 134
Paclitaxel	33069-62-4	L01CD01	95 814 310
Docetaxel	114977-28-5	L01CD02	124 378 782
Doxorubicin	23214-92-8	L01DB01	33 979 662
Daunorubicin	20830-81-3	L01DB02	2 458 616
Epirubicin	56420-45-2	L01DB03	27 800 798
Platinum containing			
Cisplatin	15663-27-1	L01XA01	3 739 623
Carboplatin	41575-94-4	L01XA02	43 006 409
Oxaliplatin	61825-94-3	L01XA03	77 154 580
Other drugs, generally regarded as cytostatics			
Verteporfin	129497-78-5	L01XD02	29 557 827
Methyl aminolevulinate	33320-16-0	L01XD03	6 557 046
Imatinib	152459-95-5	L01XX28	147 807 233
Erlonitib	183321-74-6	L01XX34	22 495 394
Azathioprine	446-86-6	L04AX01	14 831 622
Bortezomib	179324-69-7	L01XX32	33 852 438

With exeption of Cyclophosphamide and Ifosfamide these compounds were seldom or never measured in the Nordic environment.

Radioactive pharmaceuticals

All drugs that emit ionising radiation are regarded as radioactive. In Sweden the use of these types of drugs are restricted under several laws and the drugs must only be prepared and used at hospitals. When a radioactive pharmaceutical has been administered (Radio treatment of tumours), the patient may not leave the hospital until the intensity of the radiation of bodily fluids have decayed not to expose other people beyond certain thresholds. The most common sources used are;

^{11}C-labelled substances, amino acids labelled with ^{11}C, ^{18}F or ^{75}Se, ^{99}mTc-apcitide, ^{121}I labelled fatty acids (^{121}I- BMIPP and ^{121}I-IPPA) and ^{99}mTc-tetrofosmin.

As a last remark on pharmaceuticals used predominately in hospitals it is also important to consider all drugs in the late developing stages, undergoing clinical phase I- and phase II trials.

5.3.3. UNN as a case study

The 30 most sold HP at the University Hospital of Northern Norway (UNN) was obtained from the Hospital Pharmacy at UNN, and they are presented in Table 4. Any environmental concern regarding these compounds was retrieved from fass.se and a summary is presented below. The known effects were used to construct a list over compounds that is recommended for future monitoring of hospital effluents.

Table 4: The 30 most sold preparations at UNN in 2007

Active substance	Preparation name	ATC	CAS	NOK	No. packages	Type of compound
Infliximab	Remicade	L04AA12		24 871 960	4 289	monoclonal antibody
Rituximab	MabThera	L01XC02		5 303 554	394	monoclonal antibody
Trastuzumab	Herceptin	L01XC03		2 469 266	386	monoclonal antibody
Abciximab	ReoPro	B01AC13		2 000 839	590	monoclonal antibody
Docetaxel	Taxotere	L01CD02	114977-28-5	1 202 471	172	
Iodixanol	Visipaque	V08AB09	92339-11-2	1 134 632	162	
Meropenem	Meronem	J01DH02	96036-03-2	942 663	300	
Piperacillin	Tazocin	J01CR05	61477-96-1	934 851	441	
Atropine	Atropin	S01FA01	51-55-8	707 611	782	
Bortezomib	Velcade	L01XX32	179324-69-7	696 876	57	
Zoledronic acid	Zometa	M05BA08	118072-93-8	696 120	247	
Doxorubicin	Caelyx	L01DB01	23214-92-8	693 764	18	
Oxaliplatin	Eloxatin	L01XA03	61825-94-3	670 154	201	
Iopromide	Ultravist	V08AB05	73334-07-3	577 754	78	
Bupivacaine	Marcain	N01BB01	38396-39-3	572 514	2 864	
Botulinium toxin	Botox	M03AX01		568 498	296	protein
Eptacog alpha	NovoSeven	B02BD08		494 698	32	coagulation factor
Paclitaxel	Paclitaxel	L01CD01	33069-62-4	469 489	133	
Tenecteplase	Metalyse	B01AD11		423 566	42	plasminogen activating factor
Paracetamol	Perfalgan	N02BE01	103-90-2	408 616	1 386	
Iohexol	Omnipaque	V08AB02	66108-95-0	405 111	38	
Cephalotin	Cefalotin	J01DB03	153-61-7	397 021	800	
Irinotecan	Campto	L01XX19	97682-44-5	377 896	203	
Gentamicin	Gensumycin	J01GB03	1403-66-3	368 278	171	
Remifentanil	Ultiva	N01AH06	132875-61-7	350 466	539	
Morphine	Morfin	N02AA01	57-27-2	345 465	1 695	
Alteplase	Actilyse	B01AD02		342 703	142	enzyme
Cephotaxime	Cefotaxim	J01DD01	63527-52-6	316 733	846	

With exeption of Paracetamol these compounds were seldom or never measured in the Nordic environment.

From the compounds in Table 4, the monoclonal antibodies Infliximab, Rituximab, Trastuzumab, Abciximab, Buotulinium toxin, Eptacog alpha, Tenecteplase, and Alteplase are exepted from further discussions due to their structural complexity.

Drugs used in hospitals are in some cases newly approved and their environmental effects are thus not known, as no ecotoxicological investigations on these substances has not yet been conducted. Except for paracetamol, PEC/PNEC has not been calculated for the drugs presented in Table 4. However, a search for all substances in www.fass.se was done to reveal if any known environmental effects are known for these substances. No ranking among the drugs discussed here is done. Some structurally closely related substances are discussed simultaneously, as they are expected to behave in a similar manner.

The available ecotoxicological data does not exclude any potential environmental effects of **Docetaxel** and **Paclitaxel**. For **Docetaxel**, the EC50 (48 h) is 3700 µg/L for *Daphnia magna* and the EC50 (72 h) is 545 µg/L for the algae *Scenedesmus subspicatus*, whereas for **Paclitaxel**, a NOEC of 740 µg/L is reported for *Daphnia*.
Docetaxel is slowly degraded ($t_{1/2}$ hydrolysis, pH 7, is 28 d) and bioaccumulation cannot be excluded. **Paclitaxel** is readily biodegraded.

Meropenem is a typical hospital antibacterial agent. The available ecotoxicological data does not exclude any potential environmental effects of **Meropenem**. For *Daphnia magna* an EC50 (48 h) of >900 mg/L is reported. **Meropenem** is not readily degraded (abiotic and biotic), and a log P of <0.001 suggests a low risk for bioaccumulation.
There are no ecotoxicological and degradation data available for **Piperacillin**, and the log P of <-2.0 suggests a low probability for bioaccumulation.
The ecotoxicological effect of **Bortezomib** has been investigated for several species. An EC50 (72 h) of 0.30 mg/L is reported for the green alga *Scenedesmus subspicatus*, and an EC50 (48 h) of 0.45 mg/L for *Daphnia magna*. Finally, a NOEC of 0.46 mg/L was reported for the Zebra fish (*Brachydanio rerio*), yielding a PEC/PNEC ratio of 0.1. No information is available for degradation and potential for bioaccumulation

Zoledronic acid and its ecotoxicological effects are somewhat studied, and an EC50 of 5.1 mg/L and 18.0 mg/L is reported for the green algae *Selenastrum capricornutum* and *Daphnia magna*, respectively. For fish, no data exists.

For **Doxorubicin**, a PEC/PNEC of 0.0000146 is calculated, based on the reported EC50 of 9.900 µg/L for *Daphnia magna*. No degradation or bioaccumulation data exists for **Doxorubicin**.

Ecotoxicological testing of **Oxaliplatin** has only been conducted towards bacteria. **Oxaliplatin** is potentially persistent with 0% degradation observed after 28 days (OECD301B), and the abiotic hydrolysis $t_{1/2}$ at 25°C is 27.4 d at pH 7.

Cephotaxime has a PEC/PNEC of 0.000075, based on a EC50 (96 h) of >500 000 µg/L for Zebrafish, *Danio rerio*. The medicine is potentially persistent with a 13% degradation in 28 days, however, the substance is light sensitive. The substance is unlikely to bioaccumulate in aquatic organisms based on its solubility (550 000 mg/L) and pharmacokinetic properties (rapidly excreted in urine, with an elimination half-life of about 1-2 hours).

Paracetamol, **Iodixanol**, **Iopromide**, and **Iohexol** are previously discussed. No ecotoxicological relevant information is available for **Atropine, Bupivacaine, Cephalotin, Irinotecan, Gentamicin**, **Remifentanil**, and **Morphine**.

From this, the compounds **Docetaxel**, **Meropenem**, **Oxaliplatin**, and **Cephalotin** should be selected for future monitoring. However, this is not a final conclusion and the latest information on use and compound properties including information on analytical methods should be discussed before selecting compounds for hospital screening.

5.3.4. Results from the SFT-study 2006

In a SFT study in 2006 the occurrence of twenty pharmaceutical compounds was quantitatively determined in effluents from two major Oslo city hospitals, Rikshospitalet and Ullevål, along with influent, sludge and final effluent from the city's VEAS wastewater treatment works (WTW). The influent into VEAS WTW contained all of the same selected substances detected in the hospital effluents except for **Oxytetracycline**, **Chlorotetracycline**, **Demeclocycline**, **Cyclophosphamide,** and **Ifosfamide**. The percentage of pharmaceuticals entering the works from the hospitals was <10% for all of the selected compounds (Thomas, Langford et al. 2007).

5.4. Human pharmaceuticals prioritised for further monitoring

5.4.1. Prioritisation based on measured effects

Human pharmaceuticals chosen for further investigation are presented in Table 5 to Table 9. The compounds presented inTable 5 and Table 6 represent those compounds prioritised based upon measured PNEC data whilst those in Table 8 and Table 9 have a greater element of uncertainty since the risk quotients were derived using QSAR generated $PNEC_{ECOSAR}$. All compounds with a risk quotient greater than 0.01 were prioritised using a precautionary approach allowing for a high acute/chronic ratio (ACR). The ecotoxicity of the pharmaceuticals prioritised for further monitoring in Norway are summarised in Table 7.

Table 5: Estimated risk quotients for human pharmaceuticals prioritised for further monitoring in Norway based upon 2006 consumption data and measured PNEC.

Name	CAS	ATC	Sold amount [kg]	PEC [µg/l]	PNEC [µg/l]	PEC/ PNEC
Estradiol[1]	50-28-2	G03AA03	28	0.01	0.00002	413.53
Amoxicillin[1]	26787-78-0	J01CA04	1880	0.55	0.0037	148.71
Penicillin G[1]	61-33-6	J01CE01	1588	0.46	0.006	77.44
Ciprofloxacin[1]	85721-33-1	J01MA02	946	0.28	0.005	55.38
Ethinylestradiol[1]	57-63-6	G03CA01	2	0.00	0.00002	31.30
Propranolol[2]	525-66-6	C07AA05	367	0.11	0.005	21.48
Paracetamol[1]	103-90-2	N02BE01	173548	50.79	9.2	5.52
Fluoxetine[2]	54910-89-3	N06AB03	61	0.02	0.004	4.44
Diclofenac[1]	15307-86-5	M01AB05	1471	0.43	0.1	4.31
Spiramycin[1]	8025-81-8	J01FA02	65	0.02	0.005	3.80
Estriol[1]	50-27-1	G03CA04	9	0.00	0.00075	3.51
Sertraline[2]	79617-96-2	N06AB06	581	0.17	0.056	3.04
Sulfamethoxazole[1]	723-46-6	J01EE01	179	0.05	0.0268	1.96
Atorvastatin[1]	134523-00-5	C10AA05	864	0.25	0.13	1.95
Naproxen[2]	22204-53-1	M01AE02	3814	1.12	0.64	1.74
Ibuprofen[1]	15687-27-1	M01AE01	31249	9.14	7.1	1.29
Allopurinol[1]	315-30-0	M04AA01	1810	0.53	0.45	1.18
Amitriptyline	50-48-6	N06AA09	292	0.09	0.081	1.05
Tetracycline[1]	60-54-8	J01AA07	1059	0.31	0.31	1.00
Pivmecillinam[1]	32886-97-8	J01CA08	1487	0.44	0.6	0.73
Ofloxacin[2]	82419-36-1	J01MA01	28	0.01	0.014	0.59
Norethisterone[2]	68-22-4	G03AA05	17	0.01	0.01	0.51
Oxytetracycline[1]	79-57-2	J01AA06	317	0.09	0.2	0.46
Erythromycin[1]	114-07-8	J01FA01	2416	0.71	2	0.35
Carbamazepine[2]	298-46-4	N03AF01	3488	1.02	4.92	0.21
Metoprolol[1]	37350-58-6	C07AB02	6047	1.77	8.8	0.20
Glucosamine[1]	3416-24-8	M01AX05	13229	3.87	31.5	0.12
Metformin[1]	657-24-9	A10BD03	36379	10.65	101	0.11
Alendronic acid[1]	66376-36-1	M05BA04	139	0.04	0.46	0.09
Verapamil[2]	52-53-9	C08DA01	1352	0.40	5.78	0.07
Simvastatin[2]	79902-63-9	C10AA01	2166	0.63	9.6	0.07
Carvedilol[1]	72956-09-3	C07AG02	204	0.06	0.99	0.06
Bicalutamide[1]	90357-06-5	L02BB03	154	0.04	1	0.04
Oxazepam[2]	604-75-1	N05BA04	602	0.18	4.3	0.04
Paroxetine[2]	61869-08-7	N06AB05	155	0.05	1.6	0.03
Trimethoprim[1]	738-70-5	J01EA01	1373	0.40	16	0.03
Phenoxymethylpenicillin[1]	87-08-1	J01CE02	14804	4.33	177	0.02
Citalopram[2]	59729-33-8	N06AB04	301	0.09	4.9	0.02
Ezetimibe[1]	163222-33-1	C10AX09	7	0.00	0.13	0.02
Diazepam[1]	439-14-5	N05BA01	177	0.05	4.3	0.01
Fluticasone[1]	90566-53-3	R01AD08	18	0.01	0.48	0.01
Furosemide[2]	54-31-9	C03CA01	1466	0.43	45.14	0.01
Midazolam[1]	59467-70-8	N05CD08	5	0.00	0.2	0.01
Clarithromycin[1]	81103-11-9	J01FA09	336	0.10	18.7	0.01

[1]: Frequently measured in the Nordic environment.
[2]: Occasionally measured in the Nordic environment.
[1]: Seldom or never measured in the Nordic environment.

Table 6: Estimated risk quotients for human pharmaceuticals prioritised for further monitoring in Sweden based upon 2006 consumption data and measured PNEC.

Name	CAS	ATC	Sold amount [kg]	PEC [µg/l]	PNEC [µg/l]	PEC/ PNEC
Ethinylestradiol[1]	57-63-6	G03AA03	ca 70	0.011	0.0002	52.50
Propranolol[2]	525-66-6	C07AA05	1104.2	0.166	0.005	33.13
Diclofenac[1]	15307-86-5	M01AB05	3995	0.599	0.1	5.99
Ethinylestradiol[1]	57-63-6	G03AA03	4	0.0006	0.0002	2.85
Amoxicillin[1]	26787-78-0	J01CA04	5786	0.868	0.078	11.13
Fluoxetine[2]	54910-89-3	N06AB03	295.8	0.044	0.004	11.09
Paracetamol[2]	103-90-2	N02BE01	410669	61.60	9.2	6.70
Sertraline[2]	79617-96-2	N06AB06	2456	0.369	0.056	6.58
Sulfamethoxazole[1]	723-46-6	J01EE01	1175	0.1762	0.0268	6.58
Estriol[1]	50-27-1	G03CA04	32.5	0.0049	0.00075	6.51
Azithromycin[1]	83905-01-5	J01FA10	81.5	0.012	0.0044	2.78
Naproxen[2]	22204-53-1	M01AE02	11582	1.737	0.64	2.71
Ibuprofen[1]	15687-27-1	M01AE01	74274	11.141	7.1	1.57
Allopurinol[1]	315-30-0	M04AA01	3775	0.566	0.45	1.26
Amitriptyline[1]	50-48-6	N06AA09	563.1	0.0855	0.081	1.04
Acetylsalicylic acid[1]	50-78-2	N02BA51	90756	13.613	15	0.91
Atorvastatin[1]	134523-00-5	C10AA05	594.6	0.089	0.13	0.69
Metformin[1]	657-24-9	A10BD03	86903	13.036	20	0.65
Ciprofloxacin[1]	85721-33-1	J01MA02	2113	0.317	0.52	0.61
Tetracycline[1]	60-54-8	J01AA07	805.2	0.121	0.31	0.39
Salbutamol[1]	35763-26-9	R03CC02	92.5	92.474	243	0.38
Pivmecillinam[1]	32886-97-8	J01CA08	996.6	0.150	0.6	0.25
Carbamazepine[2]	298-46-4	N03AF01	7228	1.084	4.92	0.22
Estradiol[1]	50-28-2	G03CA03	14.4	0.002	0.01	0.22
Oxytetracycline[1]	79-57-2	J01AA06	258.9	0.039	0.2	0.19
Erythromycin[1]	114-07-8	J01FA01	1555	0.233	2	0.12
Glucosamine[1]	3416-24-8	M01AX05	15233	2.285	31.5	0.07
Simvastatin[2]	79902-63-9	C10AA01	3412	0.512	9.6	0.05
Alendronic acid[1]	66376-36-1	M05BA04	170.4	0.026	0.5	0.05
Citalopram[2]	59729-33-8	N06AB04	1659	0.249	4.9	0.05
Ezetimibe[1]	163222-33-1	C10AX09	42.6	0.006	0.13	0.05
Verapamil[2]	52-53-9	C08DA01	1550	0.233	5.78	0.04
Bicalutamide[1]	90357-06-5	L02BB03	229.2	0.034	1	0.03
Lithium[1]	7439-93-2	N05AN01	871.8	0.131	4.18	0.03
Carvedilol[1]	72956-09-3	C07AG02	185.9	0.028	0.99	0.03
Metoprolol[1]	37350-58-6	C07AB02	10905	1.636	58.3	0.03
Paroxetine[2]	61869-08-7	N06AB05	255.7	0.038	1.6	0.02
Phenoxymethylpenicillin[1]	87-08-1	J01CE02	28036	4.206	177	0.02
Salmeterol[1]	89365-50-4	R03AK06	439.3	0.066	2.8	0.02
Oxazepam[2]	604-75-1	N05BA04	639	0.096	4.3	0.02
Hydroxychloroquine / Chloroquine[1]	118-42-3/ 54-05-7	P01BA02, P01BA01	393.6	0.059	2.72	0.02
Furosemide[2]	54-31-9	C03CA01	6476	0.972	45.14	0.02
Ofloxacin[2]	82419-36-1	J01MA01	10.8	0.002	0.1	0.02
Tramadol[1]	27203-92-5	N02AX02	6619	0.993	64	0.02
Thioridazine[1]	50-52-2	N05AC02	27.8	0.004	0.27	0.02
Atenolol[1]	29122-68-7	C07AB03	5160	0.774	77.7	0.01
Omeprazole[1]	73590-58-6	A02BC05	2191	0.329	41.9	0.01
Trimethoprim	738-70-5	J01EA01	720	0.108	16	0.01
Diazepam[1]	439-14-5	N05BA01	173.2	0.026	4.3	0.01

[1]: Frequently measured in the Nordic environment.
[2]: Occasionally measured in the Nordic environment.
[1]: Seldom or never measured in the Nordic environment.

Table 7: Ecotoxicological tests of pharmaceuticals prioritised for further monitoring in Norway. The compounds with PEC/PNEC are presented and ranked according to the PEC/PNEC risk score estimated in the present study.

Compound	PNEC (µg/L)	Test	Duration	Reference
Estradiol	0.00002	Fish, induced intersex (*Oryzias latipes*)	risk assessment	Swedish Medical Products Agency (2004)
Amoxicillin	0.0037	Algal toxicity	7d	Lutzhoft 1999
Benzylpenicillin	0.006	Algal toxicity (*M. aeruginosa*)	7d	Halling-Sorensen 2000
Ciprofloxacin	0.005	Toxicity on fish, algae, and daphnia. Lowest for algae (*M. aeruginosa*)	risk assessment	Grung 2007
Ethinylestradiol	0.00002	Fish early life cycle (*P. promelas*)		fass.se
Propranolol	0.005	Reproduction (*O. latipes*)	28d	fass.se
Paracetamol	9.2	Invertebrate toxicity (*Streptocephalus proboscideus*)	risk assessment	Swedish Medical Products Agency (2004)
Fluoxetine	0.004	Zebra mussel spawning	not stated	Montforts (2005)
Diclofenac	0.1	Chronic effects on algae, daphnia and fish, fish lowest	risk assessment	Grung 2007
Spiramycin	0.005	Algal toxicity	7d	Halling-Sorensen 2000
Estriol	0.00075	Fish, induced intersex (*Oryzias latipes*)	risk assessment	Swedish Medical Products Agency (2004)
Sertraline	0.056	Toxicity, *D. magna*	48h	fass.se
Sulfamethoxazole	0.0268	Algal toxicity (cyanobacteria)	96h	fass.se
Atorvastatin	0.13	Algal toxicity (*L. gibba*)	7d	Brain 2004
Naproxen	0.64	Toxicity on invertebrates (*C. dubia*)	7d	fass.se
Ibuprofen	7.1	Algal toxicity	48h	fass.se
Allopurinol	0.45	Algal toxicity	96h	fass.se
Amitriptyline	0.081	Algal toxicity	72h	fass.se
Tetracycline	0.31	Algal toxicity (cyanobacteria)	not stated	fass.se
Pivmecillinam	0.6	Algal toxicity (cyanobacteria)	72h	fass.se
Ofloxacin	0.014	Algal toxicity (cyanobacteria)	72h	Backhaus (2000)
Norethisterone	0.01	See Estradiol	24h	fass.se,
Oxytetracycline	0.2	Algal toxicity and *D. magna* reproduction		Swedish Medical Products Agency (2004)
Erythromycin	2.0	Algal toxicity	risk assessment	fass.se
Carbamazepine	4.92	Crustacean reproduction	40h	Ferrari (2004)
Metoprolol	8.8	Acute toxicity invertebrates	risk assessment	Swedish Medical Products Agency (2004)
Glucosamine	31.5	Algal toxicity	72h	fass.se
Metformin	101	Not stated in report		Ayscough (2000)
Alendronic acid	0.46	Not stated in report		Ayscough (2000)
Verapamil	5.78	Not stated in report		Ayscough (2000)
Simvastatin	9.6	Algal toxicity	72h	fass.se
Carvedilol	0.99	Algal toxicity	96h	fass.se

5.4.2. Prioritisation based on theoretical estimated effects

The following human pharmaceutical substances (Table 8 andTable *9*) have been identified as especially important to highlight for environmental monitoring following ECSAR-based PEC/$PNEC_{ECOSAR}$ risk characterisation.

Non-listed human pharmaceuticals

The assessment performed has used predominantly PNECs based on acute bioassays or non-specific chronic bioassays, which do not reflect the high ACRs often seen with pharmaceutical substances. In adopting a precautionary approach it is also proposed that any screening/monitoring also includes the following compounds since they have known occurrence or known chronic effect:

Tamoxifen (L02BA01) has known environmental occurrence and known anti-estrogenic effects.

Table 8: Estimated risk quotients for human pharmaceuticals prioritised for further monitoring in Norway based upon 2006 consumption data and QSAR derived $PNEC_{ECOSAR}$

Name	CAS	ATC	Sold amount [kg]	PEC [µg/l]	$PNEC_{ECOSAR}$ [µg/l]	PEC/PNEC
Codeine	76-57-3	N02AA59	2373	0.694	0.1	11.57
Carisoprodol	78-44-4	M03BA02	4993	1.461	1.6	0.92
Acetylcysteine	616-91-1	R05CB01	2850	0.834	1.2	0.70
Nifedipine	21829-25-4	C08CA05	320	0.094	0.2	0.54
Venlafaxine	93413-69-5	N06AX16	1066	0.312	0.9	0.35
Dicloxacillin	3116-76-5	J01CF01	1789	0.524	4.8	0.11
Doxazosin	74191-85-8	C02CA04	22	0.007	0.1	0.11
Clindamycin	18323-44-9	J01FF01	537	0.157	3.6	0.04
Zolpidem	82626-48-0	N05CF02	60	0.018	0.519	0.03
Zopiclone	43200-80-2	N05CF01	394	0.115	4.7	0.02
Methenamine	100-97-0	J01XX05	9188	2.689	136.0	0.0198
Cloxacillin	61-72-3	J01CF02	398	0.116	27.8	0.0042
Lymecycline	992-21-2	J01AA04	459	0.134	45.4	0.0030
Ampicillin	69-53-4	J01CA01	345	0.101	45.7	0.0022
Isosorbide	16051-77-7	C01DA14	687	0.201	265.0	0.0008
Bendroflumethiazide	73-48-3	C03AA01	29	0.008	23.0	0.0004
Bumetanide	28395-03-1	C03CA02	15	0.004	57.7	0.0001

These compounds were seldom or never measured in the Nordic environment.

Table 9: Estimated risk quotients for human pharmaceuticals prioritised for further monitoring in Sweden based upon 2006 consumption data and QSAR derived $PNEC_{ECOSAR}$

Name	CAS	ATC	Sold amount [kg]	PEC [µg/l]	$PNEC_{ECOSAR}$ [µg/l]	PEC/ PNEC
Codeine	76-57-3	N02AA59	1617	0.24	0.06	4.04
Zolpidem	82626-48-0	N05CF02	4260.7	0.64	0.519	1.23
Norethisterone	68-22-4	G03AA05	42	0.006	0.01	0.63
Venlafaxine	93413-69-5	N06AX16	2035	0.31	0.888	0.344
Carisoprodol	78-44-4	M03BA02	2365	0.35	1.592	0.223
Nifedipine	21829-25-4	C08CA05	189.5	0.028	0.172	0.165
Clindamycin	18323-44-9	J01FF01	1724	0.259	3.614	0.072
Doxazosin	74191-85-8	C02CA04	24.43	0.004	0.061	0.060
Flucloxacillin, Cloxacillin, +Dicloxacillin (summed amount)[a]	5250-39-5/ 61-72-3/ 3116-76-5	J01CF05, J01CF02, J01CF01	9723	1.458	27.821	0.052
Methenamine	100-97-0	J01XX05	15497	2.325	136	0.02
Zopiclone	43200-80-2	N05CF01	452.3	0.068	4.747	0.015
Lymecycline	992-21-2	J01AA04	2300	0.345	45.413	0.008

These compounds were seldom or never measured in the Nordic environment.

5.5. Sampling strategy and analytical methods

The strategies presented are based on the scenarios described and summarised in Table 10.

Human pharmaceuticals

Studies have shown that the main source of human pharmaceuticals into the aquatic environment is via discharges from the wastewater collection and treatment system. The measurement of human pharmaceuticals in these samples is important in order to establish the quantities entering the environment and to validate the assumptions made during prioritisation (i.e. PECs). Hospitals, landfill sites and sites of manufacture are also potential sources. It is therefore recommended that the following are considered during any screening study:

- Effluent discharges from wastewater treatment works (WTW)
- Sludge from WTW
- Receiving environments for sludge and effluent
- Receiving water bodies and compartments therein (transect away from the point of discharge with appropriate control sites)
- Any land-based disposal

If further resolution is required then it is recommended that the following inputs are also considered:

- Hospital effluents
- WTW influents
- Landfill site leachate discharges
- Sites of pharmaceutical manufacture (for site specific analysis)
- Storm water overflow systems (during period of high precipitation)

Sampling resolution: Temporal variation is high therefore daily composites are recommended for general sampling whilst further resolution can be obtained by increasing the sampling frequency if necessary.

Analytical possibilities

For most of the substances prioritised analytical techniques have been published and are available (see Table 11). The compounds are presented in no particular order, but loosely based on the PEC/PNEC lists from Norway and Sweden. The only substances, which there are no methods available in the primary literature, are: **Pivmecillinam**, **Glucosamine**, **Alendronic acid**, and **Carvediol**.

Table 10: Summary describing sampling scenarios to be considered

	HP	PCP	Narcotics	VP Land	VP	Aquaculture
WTW influent						
WTW effluent						
WTW sludge						
Storm water overflow						
Hospitals						
Landfill sites						
Factories (pharma)						
Receiving waters						
Receiving Fields						
Farms						
Aquaculture facilities						

Key:

- Minimum sampling requirements
- Improved resolution
- Complete overall picture

Table 11: Overview over available analytical methods and limit of detection in sewage water for human pharmaceuticals prioritised for further monitoring in Norway.

Name	CAS	Extraction	Quantification	LoD [ng/l]	Remarks
Estradiol	50-28-2	SPE	LC/MS-ESI(-)	0.003 – 1	
Amoxicillin	26787-78-0	SPE	LC/MS-ESI(+)	15 – 20	
Penicillin G	61-33-6	SPE	LC/MS-ESI(+)	0.04 – 1	
Ciprofloxacin	85721-33-1	SPE	LC/MS-ESI(+)	20 – 40	
Ethinylestradiol	57-63-6	SPE	LC/MS-ESI(-)	0.02 – 1	
Propranolol	525-66-6	SPE	LC/MS-ESI(+)	10 – 20	
Paracetamol comb.	103-90-2	SPE	LC/MS-ESI(+)	40 – 50	
Fluoxetine	54910-89-3	SPE/LPME	LC/MS-ESI(+)	10 - 20	
Diclofenac	15307-86-5	SPE	LC/MS-ESI(+)	10 - 20	
Estriol	50-27-1	SPE	LC/MS-ESI(-)	1	
Sertraline	79617-96-2	SPE/LPME	LC/MS-ESI(+)	20 - 50	
Sulfamethoxazole	723-46-6	SPE	LC/MS-ESI(+)	0.1 - 50	Nebot 2007
Atorvastatin	134523-00-5	SPE, pH~4,5	LC/MS-ESI(+)	0.1 - 5	Hernando 2007
Naproxen	22204-53-1	SPE	LC/MS-ESI(+)	20 - 50	Radjenovic 2007
Ibuprofen	15687-27-1	SPE	LC/MS-ESI(-)	20 - 50	
Allopurinol	315-30-0				
Amitriptyline	50-48-6	SPE/LPME	LC/MS-ESI(+)		
Tetracycline	60-54-8	SPE	LC/MS-ESI(+)	10 - 20	
Pivmecillinam	32886-97-8				
Ofloxacin	82419-36-1	SPE	LC/MS-ESI(+)	20 – 40	
Oxytetracycline	79-57-2	SPE	LC/MS-ESI(+)	10 - 20	
Erythromycin	114-07-8	SPE	LC/MS-ESI(-)	10 - 20	
Carbamazepine	298-46-4	SPE/LPME	LC/MS-ESI(-)	0.5 - 2	Radjenovic 2007
Metoprolol	37350-58-6	SPE	LC/MS-ESI(-)	2 – 6	Radjenovic 2007
Glucosamine	3416-24-8				
Metformin	657-24-9				
Alendronic acid	66376-36-1				
Verapamil	52-53-9	SPE	LC/MS-ESI(+)	20 - 50	
Simvastatin	79902-63-9	SPE	LC/MS-ESI(+)	0.1 - 5	Hernando 2007
Carvedilol	72956-09-3				
Bicalutamide	90357-06-5				
Oxazepam	604-75-1	SPE	LC/MS-ESI(+)	20 - 50	
Paroxetine	61869-08-7	SPE/LPME	LC/MS-ESI(+)	20 - 50	
Trimethoprim	738-70-5	SPE	LC/MS-ESI(+)	0.5 - 2	Radjenovic 2007
Phenoxymethyl-penicillin	87-08-1	SPE	LC/MS-ESI(+)	0.04 – 1	
Citalopram	59729-33-8	SPE/LPME	LC/MS-ESI(+)	0.2 – 0.6	Vasskog 2006
Ezetimibe	163222-33-1				
Diazepam	439-14-5	SPE	LC/MS-ESI(+)	1 - 20	Castiglioni 2005
Fluticasone	90566-53-3				
Furosemide	54-31-9	SPE	LC/MS-ESI(-)	1 - 3	Castiglioni 2005
Midazolam	59467-70-8	SPE/LPME	LC/MS-ESI(-)		
Clarithromycin	81103-11-9	SPE	LC/MS-ESI(-)		

6. Veterinary pharmaceuticals

6.1. Introduction

HPs are generally more extensively studied than VPs, and this is reflected in the available information on the ecotoxicological effects of VPs. As a consequence, PEC/PNEC risk factors are not as reliable for VP as they are for HPs.

6.2. Environmental occurrence, fate, and effects of veterinary pharmaceuticals

6.2.1. QJ Anti-infectives for Systemic Use

Antibacterials are extensively used as veterinary pharmaceuticals. In Denmark, approximately 91 tons of antibiotics were used in the agricultural industry in 2001 (Boutrup, Fauser et al. 2006). The numbers for the other Nordic countries are expected to be lower.

QJ01A Tetracyclines

Relevant substances: mode of action and pharmacokinetics

Tetracyclines are a group of substances representing high use in the Swedish veterinary medicine. For additional information, please see the analogous section under Human pharmaceuticals.

Results from previous screenings

Please see the analogous section under Human pharmaceuticals.

Relevant environmental properties, ERA, and monitoring recommendations

About half of the total consumption of tetracyclines in veterinary applications is estimated to be used in gross administration to groups of animals, which means that the emissions can have a much higher concentration compared to cases where one or a couple of animals are being treated simultaneously. In Norway the use is about half that of Sweden. Tetracyclines have showed to be rather stable in the environment and they possess a strong sorption (adsorption or complex binding seems to be predominant) to soil, thus even the storage and ripening of manure and dung may not decrease the residual concentrations enough to decrease the risks of emission (Russell 1989; Loke 2002). The major degradation pathway seems to be photo degradation. The individual drug chosen for monitoring in Sweden from this group is **Oxytetracycline** (CAS 79-57-2). **Oxytetracycline** is strongly adsorbed to soil (Koc, sandy loam =60,963, (Russell 1989; Loke 2002). In Sweden it is being administrated mainly for group treatment of cattle, pigs and fish. The annual veterinary consumption is approximately 650 kg and the substance is also sold as a human pharmaceutical (~260 kg), thus an annual emission of at least 900 kg can be anticipated in Sweden. **Oxytetracycline** (QJ01AA06) is ranked 4th and **Doxycycline** 27th in the ERA ranking. For VPs, however, **Tetracycline** and **Oxytetracycline** are primarily recommended monitored as HPs.

Analytical strategy

SPE for aqueous samples and LLE for solid samples, followed by LC-MS.

QJ01C Beta-lactam anti-bacterial agents , penicillins

Relevant substances: mode of action and pharmacokinetics

Please see the analogous section under Human pharmaceuticals.

Results from previous screenings

No compounds from this class of VPs have been detected in the Nordic environment.

Relevant environmental properties, ERA, and monitoring recommendations

This group of drugs is very frequently used and several of the compounds show an elevated toxicity towards especially algae. However they are seldom encountered in environmental monitoring studies, which could indicate a rapid biodegradation. The emission routes most probably associated with environmental risks are leakage from urine reservoirs and leaching from manure from pasturing animals into nearby water recipients. The individual drug chosen for monitoring in Sweden and Norway from this group is **Amoxicillin** (CAS 26787-78-0), ranking as 5th. **Amoxicillin** is being administrated to almost all types of animals in both Sweden and Norway and group administration of whole herds occurs. Roughly 770 and 530 kg of **Amoxicillin** was used in veterinary applications in Sweden and Norway in 2006 respectively. The drug is also sold as a human pharmaceutical (~4800 kg in Sweden), thus an annual emission of at least 5550 kg can

be anticipated in Sweden. According to fass.se **Amoxicillin** is slowly degraded in the environment. It is reported to be *inherently biodegradable* according OECD 302B, with a $t_{½}$ (*hydrolysis*) of 50-113 d at pH 7 (OECD 111), and a t½ (*photolysis*) of 1.13 days at pH 7.5 and 25°C.

Analytical strategy
SPE for aqueous samples and LLE for solid samples, followed by LC-MS.

QJ01E Sulfonamides and Trimethoprim
Relevant substances: mode of action and pharmacokinetics
The antibacterials described here exhibit similar mechanisms of action as their J01 analogous described above for HPs. Sulfonamides are frequently used as antimicrobial/antibacterial drugs for cattle, pigs, horses and sheep, and are also used as antiparasitic drugs for poultry (**Sulfaclozin**, 47 kg annually in Sweden). They are partially metabolised.

Results from previous screenings
Sulfadiazine (QJ01E W10) has been detected in swine manure in Denmark (Jacobsen and Halling-Sørensen 2006) and in stream water in Norway (Møskeland 2006), at concentrations in the same range or above PNEC
Sulfadoxine (QJ01E W13.) has been detected in swine manure in Denmark (Jacobsen and Halling-Sørensen 2006) and Sweden (Lindberg 2005), as has **Sulfamethazine** (QJ01EB03).

Relevant environmental properties, ERA, and monitoring recommendations
Sulfonamides are considered as very mobile in the environment due to high water solubility and low log Kow-values. Sulfonamides can be expected to percolate to the ground water and the substances are generally very stabile in aqueous media. Sulfonamides for antibacterial use are always sold as combination drugs with **Trimethoprim**. Sulfonamides are especially toxic to algae. **Sulfamethazine** gave abnormal growth and development of *Crassostrea virginica* (American oyster) embryos at an EC50 of >600 mg/L over 48 hr (NIH 2007). A log P of 0.14, indicate that **Sulfamethazine** is not expected to adsorb to suspended solids and sediment. The pKa of **Sulfamethazine** is 7.49, indicating that this compound will exist partially as an anion in the environment. **Sulfamethazine** has an estimated BCF of 0.8, suggesting the potential for bioconcentration in aquatic organisms is low. **Sulfamethazine** was completely degraded within 20 days in activated sludge systems, indicating that this substance may undergo biodegradation in water. However, less than 1% degradation after 64 days in loamy sand and clay silt suggests that biodegradation will be slow under certain conditions (NIH 2007).
Sulfadiazine has an EC50 of 135 µg/L over 72 h towards the blue-green algae *Microcystis aeruginosa*, and is ranked second in both the Norwegian and Swedish veterinary medicine ecotoxicological assessments conducted in the present study.
Sulfadoxine is consumed in amounts of 88 kg in Norway and 500 kg in Sweden annually while no ecotoxicity data have been found in open literature. This substance could therefore also be of interest in future monitoring programmes, especially since it has been detected in Swedish ground water samples
The individual drugs chosen for monitoring in Sweden and Norway from this group are thus **Trimethoprim** and **Sulfadiazine**. The Norwegian veterinary consumption of **Trimethoprim** in 2006 was 265 kg and of **Sulfadiazine** was 1290 kg. These quantities are in the same order of magnitude as those used in Sweden in 2006. The veterinary consumption of **Trimethoprim** amounted to 450 kg and **Sulfadiazine** 1700 kg. **Trimethoprim** is also sold as a human pharmaceutical. Both these drugs are metabolised prior to excretion and the main metabolites are hydroxylated and glucuronated (**Trimethoprim**) or acetylated and glucuronidated (**Sulfadiazine**). Neither **Trimethoprim** nor **Sulfadiazine** seems to photo-degrade (Boxall 2004).
Regarding **Trimethoprim**, fass.se reports that it is not readily or inherently biodegradable. Furthermore, based on measurements in Swedish sewage works, there was negative (probably de-conjugation) up to 40% elimination, with no elimination on the average. Based on several measurements, half-lives in the aquatic compartment are estimated at 20–100 days, and 5.7 days in a microcosm study.
Sulfadiazine is ranked 2nd, **Trimethoprim** 6th, and **Sulfathiazole** 16th, in the ecotoxicological ranking conducted in the present study, and these compound should be included in future monitoring programs.

Analytical strategy
SPE for aqueous and LLE for solid samples, followed by LC-MS for identification and quantification.

QJ01F Macrolides and lincosamides
Relevant substances: mode of action and pharmacokinetics
Tylosin A (QJ01F A90) is not approved for use in Norway.

Results from previous screenings
Tylosin A has been detected in swine manure in Denmark (Jacobsen and Halling-Sørensen 2006).

Relevant environmental properties, ERA, and monitoring recommendations
The log P of 1.63 indicates that **Tylosin** is expected to adsorb to suspended solids and sediment. **Tylosin** has a pKa of 7.50, which indicates that this compound will partially exist in the protonated form in water. **Tylosin** has an estimated BCF of 4, suggesting the potential for bioconcentration in aquatic organisms is low. No biodegradation data for **Tylosin** in water exists, however it was shown to biodegrade readily in soil. **Tylosin** contains functional groups that may hydrolyse, but no experimental data on the hydrolysis rate exists (NIH 2007). This group of veterinary drugs are almost exclusively used in group treatments of whole herds/populations (pigs and poultry) and occasionally for treatment of individual animals (pigs and cattle). Macrolides are generally metabolised only to a minor extent within the treated animals and the administrated dose can be expected to be excreted unchanged. However they are often subjected to fast biodegradation in soil and manure (Tolls 2001; Loke 2002; Boxall 2004). The individual drug chosen for monitoring in Sweden from this group is **Tylosin** (CAS 1401-69-0). Annually 980 kg of the substance is used in Sweden where dysentery and enteritis of swine are the most common indications for using the drug. The main emission routes to the environment seem to be leaching from manure especially in the case of using contaminated manure as fertilizer. **Tylosin** is not so heavily used in Norway with less than 1 kg being used per year and therefore not recommended for further monitoring in Norway.

Analytical strategy
This compound should be isolated from aqueous samples by SPE and analysed by LC-MS.

QJ01G Amino glycosides
Relevant substances: mode of action and pharmacokinetics
Amino glycosides are anti-bacterial drugs, which are not metabolised in the animals.

Results from previous screenings
These compounds have not previously been monitored in the Nordic environment.

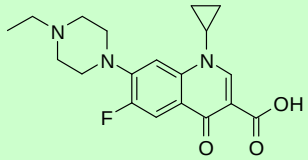
Relevant environmental properties, ERA, and monitoring recommendations
They are administered to a wide group of animals including sheep, cattle, pigs, horses and pets. There is a general lack of data concerning their biodegradation capability; however they are reported to subject to rather fast photolysis (Alexy 2004). The individual drug chosen for monitoring in both Sweden and Norway from this group is **Dihydrostreptomycin** (CAS 128-46-1). In 2006, almost 1000 kg of **Dihydrostreptomycin** was sold in Norway and half that amount in Sweden. **Dihydrostreptomycin** is very toxic to algae, and ranked 9th in the ERA conducted in the present study, and it is therefore it is especially interesting to monitor this drug in aquatic environments.

Analytical strategy
This compound should be isolated from aqueous samples by SPE and analysed by LC-MS.

QJ01M Quinolones
Relevant substances: mode of action and pharmacokinetics
Enrofloxacin (QJ01M A90), see analogous section under HPs for further information.

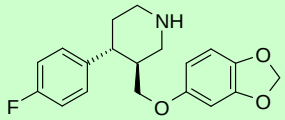
Results from previous screenings
Enrofloxacin has only been detected in Norwegian sediment (Møskeland 2006).

Enrofloxacin



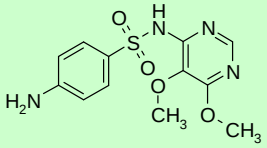
QJ01M A90, 93106-60-6
$C_{19}H_{22}FN_3O_3$, Mw=359.4039
pKa=6.06; 7.7, log D= 1.28

Sulfadiazin



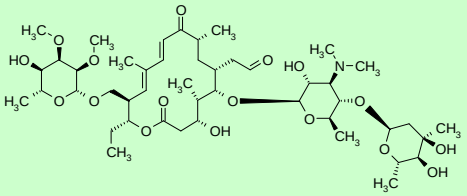
QJ01E W10, 68-35-9
$C_{10}H_{10}N_4O_2S$, Mw=250.3
pKa=1.57; 6.15, log D=-0.092

Sulfadoxine



P01BD01 QJ01E W13., 2447-57-6
$C_{12}H_{14}N_4O_4S$, Mw=310.3
pKa=1.59, log D=-0.53

Tylosin A



QJ01F A90, 1401-69-0
$C_{46}H_{77}NO_{17}$, Mw=916.1
pKa=3.31; 7.50, log D=2.87

Relevant environmental properties, ERA, and monitoring recommendations
Fluoroquinolones are especially used for treatment of cattle, pigs and poultry. Group treatments are especially frequently occurring regarding poultry. Fluoroquinolones are often excreted as the mother compound (similar to macrolides) and are very persistent in the environment. Photolysis seems to be the most important degrading mechanism. The 24 h EC50 and 48h EC50 of **Enrofloxacin** to *Daphnia carinata* were 34.03 µg/mL and 19.37 µg/mL, respectively, thus **Enrofloxacin** was of medium toxicity (Wu, Wang et al. 2005). **Enrofloxacin** is ranked 11th in the ERA conducted in the present study and is recommended for further monitoring. Annually some 180 kg of **Enrofloxacin** is used in Sweden compared to 28 kg in Norway. Approximately 60 % of the administered dose of **Enrofloxacin** is mainly excreted unchanged (depending on the type of animal) and the main metabolite is **Ciprofloxacin**, a human pharmaceutical (CAS 85721-33-1). Most Fluoroquinolones (for human use) are reported to pass through STPs without any pronounced degradation (Alexy 2004; Lindberg 2005). **Enrofloxacin** is ranked 11th in the ERA conducted in the present project, and is recommended for further monitoring.

Analytical strategy
LC-MS preceded by SPE (aqueous) or LLE (solid) samples.

QJ01XQ Pleuomutilines
Relevant substances: mode of action and pharmacokinetics
Pleuomutilines (i.e. **Tiamulin** QJ01X Q01) are used on pigs on to treat swine dysentery

Results from previous screenings
Tiamulin has not previously been monitored in the Nordic environment.

Relevant environmental properties, ERA, and monitoring recommendations
The individual drug chosen for monitoring in Sweden from this group is **Tiamulin** (CAS 55297-95-5). In 2006 440 kg of **Tiamulin** was sold in Sweden. Only a small fraction of administered dose is excreted as the mother compound and the known metabolites are expected to have a lower ecotoxicity compared to **Tiamulin**. However, **Tiamulin** is rather toxic towards algae and this veterinary pharmaceutical is only being administered in group treatments, which imply that the local concentration at the particular swine stables can reach non- negligible levels. Both **Tiamulin** and the expected metabolites are very water soluble, thus it is interesting to monitor surface- and ground water. Less **Tiamulin** is used in Norway, only 24 kg in 2006. **Tiamulin** is ranked 8th in the ERA and is recommended for screening in close proximity of swine farms.

Analytical strategy
SPE and LLE for aqueous and solid samples, respectively, followed by LC-MS.

6.2.2. QP Antiparasitic Products, Insecticides and Repellents

QP52A Antihelminitics

QP52AC Benzimidazoles

Relevant substances: mode of action and pharmacokinetics

Fenbendazole (QP52AC13), **Oxfendazole** (QP52AC02) and **Albendazole** (QP52AC11) are used to treat helminitic infections.

Results from previous screenings

These compounds have not previously been monitored.

Relevant environmental properties, ERA, and monitoring recommendations

Benzimidazoles are a group of broad spectrum antihelmintic drugs used against gastro-intestinal parasites including roundworms, hookworms, whipworms, the taenia species of tapeworms, pinworms, aelurostrongylus, paragonimiasis, strongyles and strongyloides and can be administered to sheep, cattle, horses, fish, dogs, cats, and seals. Benzimidazoles are reported to be rather stable in the environment, have strong soil- and sediment sorption and no being subjected to hydrolysis in the pH-interval 5-9 (Company 1983). The individual drug chosen for monitoring in Sweden from this group is **Fenbendazole** (CAS 43210-67-9). In 2006 1000 kg of Fenbendazole was sold in both Norway and Sweden. **Fenbendazole** is toxic towards both crustaceans and fish (PNEC ~0.01 µg/L, depending on the assessment factor used). There are also a couple of structure analogues of **Fenbendazole** also being sold as veterinary drugs in both Norway and Sweden, **Oxfendazole** and **Albendazole**. **Fenbendazole** is ranked 3rd, **Oxfendazole** 12th, and **Albendazole** 21st in the ERA estimated here, and one or more of these compounds are thus recommended for future monitoring.

Analytical strategy

SPE and LLE for aqueous and solid samples, respectively, followed by LC-MS.

QP52AF Tetrahydropyrimidines

Relevant substances: mode of action and pharmacokinetics

Tetrahydropyrimidines, e.g. **Pyrantel** (QP52AF02) are used as anti-parasitic drugs (broad spectrum antihelmintic drugs) for horses and pets.

Results from previous screenings

Pyrantel has not been monitored in the Nordic environment.

Relevant environmental properties, ERA, and monitoring recommendations

The individual drug chosen for monitoring in Norway and Sweden from this group is **Pyrantel** (CAS 15686-83-6). **Pyrantel** is ranking 2nd according to the ECOSAR ERA conducted in the present study. In 2006 almost 2000 kg of **Pyrantel** was sold in Sweden and 500 kg in Norway. According to a study Pyrantel is the most commonly used anti-parasitic drugs used in horses (Lind 2005). The substance as such is insoluble in water but is administered as a pamoate (salt of pamoic acid, CAS 130-85-8). Metabolism of **Pyrantel** is incomplete (50-70 % depending on the type of animal) and there are no ecotoxicity data on the substance. **Pyrantel** is recommended for future monitoring.

Analytical strategy

SPE and LLE for aqueous and solid samples, respectively, followed by LC-MS.

QP54 Endectocides

QP54A Macrocyclic lactones

Relevant substances: mode of action and pharmacokinetics

Ivermectin (QP54A A01) works by inhibiting chloride canals in invertebrate nerve and muscle cells, leading to paralysis and death of the parasite.

Results from previous screenings

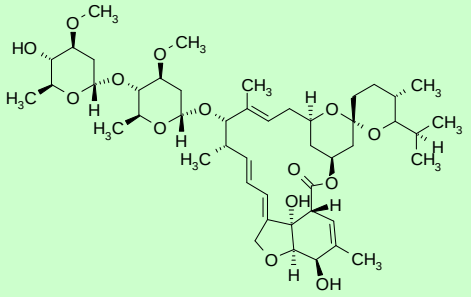
Ivermectin has been detected in reindeer manure. **Ivermectin** is persistent and of some concern (Asbakk, Hrabok et al. 2006), and was detected at concentrations in the same range or above PNEC.

Relevant environmental properties, ERA, and monitoring recommendations

The predominantly most frequently used group among the macro cyclic lactones are the avermectines (a fermentation product of the soil bacteria *Streptomyces avermitilis*). Avermectines are administrated as an anti-parasitic drug to sheep, cattle, pigs, horses and reindeers, both intravenously and externally (gels). Mostly it is treatment of individual animals rather than group treatment, thus the overall consumption is moderately low. The individual

drug chosen for monitoring in both Norway and Sweden from this group is **Ivermectin**. The overall consumption of Ivermectin in Sweden 2006 was 60 kg whilst 13 kg was used in Norway. However, Ivermectin is extremely toxic to several aquatic species, especially Crustaceans (Water-flea, e.g. *Daphnia magna*), 48 hr LC_{50} = 0.025 µg/l, Sweet water water-flea (*Gammarus* sp.), 96 hr LC_{50} = 0.033 µg/L, (Boxall 2004). EC50 of **Ivermectin** for daphnids is 25 ng/L (Halley, Nessel et al. 1989). In the ecotoxicological assessment conducted in the present study. Ivermectin is also very toxic to soil- and dung invertebrates (Boxall 2004). Ivermectin is only partially metabolised in the treated animals where one of the major metabolites seems almost as ecotoxic as the mother compound (Boxall, personal communication). Furthermore, the substance is lipophilic and strongly adsorbed to soil (Koc; 12600-15700, (Boxall 2004). Emission routes include manure and dung as well as spillage from external applications. Photo degradation seems to be the most important degradation mechanism. Considering the possible ecotoxicological effects, **Ivermectin** should be included in future monitoring programs. **Ivermectin** is ranked first based on both Norwegian and Swedish data.

Ivermectin



QP54A A01, 70209-81-3 (1B)
71827-03-7 (1A)
$C_{47}H_{72}O_{14}$(1B) Mw=861.0895 (1B)
C_{48} H_{74} O_{14} (1A),
pKa=not found, log P/D= not found

Analytical strategy
LC-MS preceded by SPE (aqueous) or LLE (solid) samples.

6.2.3. Concluding remarks on the monitoring data of veterinary pharmaceuticals.

Antibiotics are the most frequently monitored and most used VPs. The anti parasitic agent Ivermectin has been detected in reindeer faces.

6.3. Prioritisation for further monitoring

Veterinary pharmaceuticals chosen for further investigation are presented in Table 12 and Table 13.

Table 12: Sales volumes and measured PNEC data for veterinary pharmaceuticals sold in Norway and Sweden. Details regarding the Animal groups for which the veterinary pharmaceuticals are used are described in the digital supplementary material.

Monitoring Priority	Name	CAS	Sold amount [kg]		PNEC [µg/l]	ATC-code
			Norway	Sweden		
1	Ivermectin[2]	70288-86-7	13	60	0.000025	QP54AA01
2	Sulfadiazine[2]	68-35-9	1,290	1,734	0.03	QJ01EW10
3	Fenbendazole[3]	43210-67-9	1,038	1,001	0.01	QP52AC13
4	Oxytetracycline[1]	79-57-2	277	641	0.20	QJ01AA06
5	Amoxicillin[3]	26787-78-0	527	767	0.078	QJ01CR02
6	Trimethoprim[1]	738-70-5	265	450	16.0	QJ01EW10
7	Tylosin[2]	1401-69-0		981	300.0	QJ01FA90
8	Tiamulin[3]	55297-95-5	24	439	0.060	QJ01XX92,
9	Dihydrostreptomycin[3]	128-46-1	128	496	0.070	QJ01RA01
10	Penicillin G[3]	61-33-6		1,134	0.120	QJ01RA01
11	Enrofloxacin[1]	93106-60-6	28	184	10.00	QJ01MA90
12	Oxfendazole[3]	53716-50-0	175	230	0.120	QP52AC02
13	Doramectin[3]	117704-25-3	2	15	0.00003	QP54AA03
14	Phoxim[3]	14816-18-3	9	155	0.0650	QP53AF01
15	Ampicillin[3]	69-53-4	<1	142	0.0780	QJ01CA01
16	Sulfathiazole[2]	72-14-0	<1	184	10.0	
17	Ketoprofen[1]	22071-15-4	26	118	100.0	QM01AE03
18	Calcium Gluconate[3]	299-28-5	<1	3986	100.0	QA12AX
19	Meloxicam[3]	71125-38-7	12	43	50.0	QM01AC06
20	Omeprazole[2]	73590-58-6	<1	12	41.9	QA02BC01
21	Albendazole[3]	54965-21-8	238	46	0.0240	QP52AC11
22	Praziquantel[3]	55268-74-1	20	34	36.5	QP52AA51
23	Moxidectin[3]	113507-06-5		7	0.0003	QP54AB52
24	Flumethrin[3]	69770-45-2	10	15	0.2	QP53AC05
25	Spiramycin[3]	8025-81-8	<1	85	0.050	QJ01FA02
26	Valnemulin[3]	101312-92-9	<1	20	44.70	QJ01XQ02
27	Doxycycline[1]	564-25-0	<1	42	15.20	QJ01AA02
28	Permethrin[3]	52645-53-1	93	137	0.0002	QP53AC04
29	Fipronil[3]	120068-37-3	5	68	54.0	QP53AX15
30	Fusidic acid[3]	6990-06-3	<1	5	4.3	QS01AA13
31	Clotrimazole[3]	23593-75-1	<1	2	1.7	QS02CA06
32	Imidacloprid[3]	105827-78-9	2	11	13.9	QP53AX17
33	Tolfenamic acid[3]	13710-19-5	<1	3	7.4	QM01AG02
34	Deltamethrin[3]	52918-63-5	57	88	0.0018	QP53AC11

[1]: Frequently measured in the Nordic environment.
[2]: Occasionally measured in the Nordic environment.
[3]: Seldom or never measured in the Nordic environment.

Table 13: Sales volumes and modelled PNEC data for veterinary pharmaceuticals sold in Norway and Sweden

Monitoring Priority	Name	CAS	Sold amount [kg]		PNEC ECOSAR [µg/l]	ATC-codes
			Norway	Sweden		
1	Penicillin procaine	61-33-6/ 59-46-1	3372	10666.3	4.87	QJ01RA01
2	Pyrantel	15686-83-6	571	1943.8	0.18	QP52AF02
3	Sulfadoxine	2447-57-6	88	506.0	8.59	QJ01EW13
4	Phenylbutazone	50-33-9		427.7	0.26	QM01AA01
5	Metamizol	50567-35-6	31	216.8	38.2	QN02BB02
6	Cephalexin	15686-71-2		1168.4	607	QJ01DB01
7	Febantel	58306-30-2		268.7	578	QP52AA51
8	Guaifenesin	93-14-1		191.3	2.46	QM03BX90
9	Clindamycin	18323-44-9	16	175.5	8.52	QJ01FF01
10	Flunixin	38677-85-9	23	94.2	3.99	QM01AG90
11	Clavulanic acid	58001-44-8		54.0	13.3	QJ01CR02,
12	Ceftiofur	80370-57-6		26.3	189.7	QJ01DD90
13	Toltrazuril	69004-03-1	146	5.6	0.09	QP51AJ01
14	Benzathine	140-28-3		29.9	1.83	?
15	Xylazine	7361-61-7		7.3	0.64	QN05CM92
16	Propofol	2078-54-8	2	6.9	2.19	QN01AX10
17	Prednisolone	50-24-8		3.6	426	QS02CA01
18	Eprinomectin	123997-26-2	2	5.8	0.59	QP54AA04
19	Carprofen	52263-47-5	111	274.0	40.0	QM01AE91
20	Danofloxacin	112398-08-0		4.2	592	QJ01MA92
21	Medroxyprogesterone	520-85-4		22.6	10.4	QG03DA02
22	Phenylpropanolamine	14838-15-4		5.2	33.7	QG04BX91
23	Cyclosporine	59865-13-3		3.7	4.58	QL04AA01
24	Cefadroxil	50370-12-2		17.4	1,211	QJ01DB05
25	Marbofloxacin	115550-35-1		5.0	31.4	QJ01MA93
26	Selamectin	165108-07-6	4	16.8	0.28	QP54AA05
27	Flubendazole	31430-15-6		16.3	1.3	QP52AC12
28	Tepoxalin	103475-41-8		12.7	10.2	QM01AE92
29	Vedaprofen	71109-09-6	13	18.5	0.51	QM01AE90
30	Trilostane	13647-35-3		4.5	21.3	QH02CA01
31	Lufenuron	103055-07-8		3.1	0.09	QP53BC01
32	Clomipramine	303-49-1	2	2.4	0.05	QN06AA04
33	Aglepristone	124478-60-0	1	1.7	0.09	QG03XB90
34	Benazepril	86541-75-5	2	2.4	8.52	QC09AA07
35	Ibafloxacin	91618-36-9		1.3	61.9	QJ01MA96
36	Pimobendan	74150-27-9		1.3	1.3	QC01CE90

These compounds were seldom or never measured in the Nordic environment.

Some of the most frequently used veterinary drugs are, according to the Swedish sales statistics, only being administered to pets (dogs, cats, and rodents). These drugs have been given less priority in the monitoring list even though the amounts and ecotoxicity may suggest otherwise. The reason is that the local concentration of veterinary drugs in the environment from these animals will most probably be very low compared to veterinary drugs also used in the context of intensively reared husbandry that excretes the drugs (or the corresponding metabolites) in stables or pastures where the local aquatic concentration is anticipated to be very high occasionally (high concentration of animals locally, group treatments of all animals).

The veterinary drug on top of the monitoring priority list is **Ivermectin**. The total amount used in Sweden 2006 is not more than 60-70 kg and in Norway ~13 kg while the ecotoxicity of the drug is very high. Human pharmaceuticals cannot be stopped from market introduction based on hazardous environmental properties alone (instead drug efficacy, specificity and acceptable side-effects with regard to the conditions of the disease are the ruling parameters). However, veterinary drugs with high ecotoxicity alone can disqualify a substance from market introduction. It is questionable whether **Ivermectin** would have been given market permission today, given its high ecotoxicity and the current wider environmental awareness. In Table 12 the monitoring priority order of veterinary drugs with experimentally determined ecotoxicity is given and in Table 13 the corresponding ranking for veterinary drugs where ecotoxicity is assessed only by using QSAR.

In 2006 over 10 tonnes of active substances were used for veterinary application in Norway, compared to over 300 tonnes of human pharmaceuticals. In Sweden some 46 tonnes of active substance were used for veterinary application in 2006. The corresponding number for human pharmaceuticals is above 1000 tonnes.

In 2007 Norway had ~35,000 farms. Of these 20,000 kept cattle, 15,000 sheep, 3,400 pigs, 2000 chickens and 500 goats. The total livestock count for Norway in 2007 was 1,500,000 pigs, 900,000 cattle, 1,000,000 sheep and 40,000 goats. In 2004 the size of the Swedish livestock was 1,600,000 cattle, out which 22,000 were cows for dairy production (distributed over some 28,000 farms), 47,000 sheep (distributed over some 8,000 farms), and 1,900,000 pigs (distributed over some 3,200 farms). The number of horses was estimated to be around 285,000 (distributed over some 56,000 locations).

In choosing which of these veterinary drugs to prioritise for environmental monitoring there are some considerations that needs to be pointed out. The main emission pathway is the un-metabolised, or the metabolised drug being emitted from the treated animal by excretion. Contaminated dung and manure spread on agricultural land or planted forests will subsequently emit the pharmaceutical residues either by leaching or by soil run-off. Another possible route of emission is in the residual water from feeding stations, troughs and the dishing of such devices. This is route could be particularly important considering veterinary pharmaceuticals that are being administered to the animals by addition to the food or water. Veterinary drugs for external application such as several anti-parasitic drugs, could also reach the environment from rinsing of animals in stables (by passing the local STP) or on pasture. Treatments such Sheep-dips (organophosphorus compounds and pyrethroids) are assumed to be a major pathway to environmental release of veterinary drugs in Great Britain (Boxall et al., 2004).

Finally also the handling and disposal of residual veterinary drugs by the farmer could be a potential emission pathway although it is difficult to assess the magnitude of it. Residual veterinary pharmaceuticals should according to Swedish law be dealt with by the farmer in the same manner as environmentally hazardous waste. In the monitoring priority list (Table 12 and Table 13) there are a number of veterinary substances listed where environmental monitoring is called upon.

6.4. Pharmaceuticals used in aquaculture

The PECs are worst case assuming that all the material used enters the environment and that there is limited dissipation (x 100). No allowances have been made for degradation. Therefore the PECs therefore overestimate the actual environmental concentrations and it is recommended that a further tier of evaluation is performed in order to refine the reported PECs prior to performing any monitoring. It is likely that refinement of the PEC will require a location specific approach due to variations in the currents and tides at each location. What is important is that this procedure has ranked the aquaculture pharmaceuticals used in Norway.

The use of veterinary pharmaceuticals in aquaculture potentially poses a direct risk to the aquatic environment since the compounds used directly enter the environment during application and following metabolism. In Scotland environmental quality standards have been set for some of the aquaculture pharmaceuticals used which are derived from PNEC data (SEPA, 2006). Where available these PNEC data have been used.

The environmental effects of the compounds used in Norwegian aquaculture have been described in more detail in Table 15.

Table 14: Estimated risk quotients for veterinary pharmaceuticals used in Norwegian aquaculture

Compound	Amount used (kg)	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Emamectin	60	0.042	0.00022	191
Deltamethrin	23	0.016	0.00024	67
Praziquantel	145	0.102	0.028	3.7
Cypermethrin	49	0.034	0.016	2.1
Oxolinic acid	1119	0.784	0.42	1.9
Fenbendazole	27	0.019	0.027	0.70
Bronopol	49	0.034	5.90	0.0058
Flumequine	7	0.005	1.59	0.0031
Benzocaine	400	0.280	210	0.0013
Malachite green	0,9	0.001	0.66	0.0010
Isoeugenol	6,5	0.005	75.00	0.00006
Metacain	1216	0.852		

These compounds were seldom or never measured in the Nordic environment.

Table 15: Environmental tests of compounds used in aquaculture

Compound	PNEC (µg/L)	Test	Test duration	Reference
Emamectin	0.00022	Toxicity fish, invertebrate, algae	96h-21d	SEPA (1999)
Deltamethrin	0.00024	Toxicity amphibians, fish, mollusc, algae	24-96 h	www.pesticideinfo.org
Praziquantel	0.028			
Cypermethrin	0.016	Toxicity fish, crustaceans, polychaets	not given	SEPA (1998))
Oxolinic acid	0.42			
Fenbendazole	0.027	Toxicity D. magna and cyanobacteria	48-96 h	Oh *et al.* (2004)
Bronopol	5.90	Toxicity fish, mollusc, zooplankton	48-96h	www.pesticideinfo.org
Flumequine	1.59	Toxicity fish, algae, zooplankton	24-72h	www.pesticideinfo.org
Benzocaine	210	Toxicity fish (*C. carpio*)	1-96h	www.pesticideinfo.org
Malachite green	0.66	Toxicity fish, crustaceans, mollusc, algae	6h-14d	www.pesticideinfo.org
Isoeugenol	75	Toxicity daphnids	48 h	www.heraproject.com

From the data presented in Table 14 we recommend the macro cyclic lactone **Emamectin** for monitoring. The high risk quotient derived for **Emamectin** is due to a low PNEC. **Emamectin** has an EQS of 0.22 ng/L as maximum allowable concentration in receiving water body and 0.763 µg/kg as maximum allowable concentration outside the allowable zone of effects. Site specific risk assessments have been performed in Scotland, which have shown little risk to the surrounding environment following **Emamectin** use, however it is uncertain whether these scenarios apply to Norway.

The derived risk quotients for **Benzocaine**, **Praziquantel**, **Cypermethrin**, **Deltamethrin** and **Oxolinic acid** are all greater than 1. Given the localised nature of where these compounds are used and the specific patterns of use that are employed it is recommended that prior to the screening of these compounds further assessment is performed in order to refine the risk quotients based on application and use scenarios specific to Norway. Should the risk quotients still exceed 1 following the refinement of PEC with improved degradation and dispersion data then inclusion is recommended.

Aquaculture is not a major enterprise in Sweden. In 2004 there were about 100 fish farms producing Rainbow trout (*Oncorhynchus mykiss*). Their total production amounted to some 48000 tonnes, with only 10 facilities representing over 80 % of the production. A majority of the fish farms produced less than 10 tonnes annually and the production at those sites is thus being considered to be semi-professional. The veterinary drug most commonly associated with aqua culture is **Oxytetracycline** (used as a food additive) and the total consumption of **Oxytetracycline** in Swedish aqua culture amounted to 7 kg in 2004 (~1% of the amount totally used for veterinary applications and 2.6% of the amount totally used in human pharmaceuticals, data from 2006).

6.5. Sampling strategy and analytical methods for VP

Veterinary pharmaceuticals

Agriculture

It is proposed that the worst-case scenario for agriculture animals is used; over-wintering of livestock indoors. Here the waste is collected in large pits, which can be easily sampled prior to disposal to land. It is recommended that both solid and liquid phase are analysed separately and that waste from different animals is collected; pigs, cattle, sheep, deer and poultry. Since this material will be disposed of to land then it is recommended that a screening study includes soil samples following sludge application to land (and possibly after some time to estimate persistence).

Aquaculture

Any veterinary pharmaceuticals used in aquaculture will be directly released into the aquatic environment. It is proposed that any screening study measures the selected substances along a grid away from the aquaculture site preferably designed with consideration for hydrology data.

Analytical possibilities

For most of the substances prioritised analytical techniques have been published and are available.

Table 16: Summary describing sampling scenarios to be considered

	HP	PCP	Narcotics	VP Land	VP Aquaculture
WTW influent					
WTW effluent					
WTW sludge					
Storm water overflow					
Hospitals					
Landfill sites					
Factories (pharma)					
Receiving waters					
Receiving Fields					
Farms					
Aquaculture facilities					

Key:

- Minimum sampling requirements
- Improved resolution
- Complete overall picture

7. Personal care products (PCPs)

7.1. Introduction

The National Institute of Health in USA divide personal care products (PCP) into following product categories: Babies & Kids, Bath/Shower Products, Body Makeup, Cleaner, Disinfectant, Eye Care/Makeup, Face Makeup, Fragrances, Hair Care, Hair Colour, Manicuring Products, Men's Products, Oral Hygiene, Personal Cleanliness, and Skin Care. In contrast to both human and veterinary pharmaceuticals most of the PCPs are made of several different ingredients and several of those ingredients are used in more than only one product category.

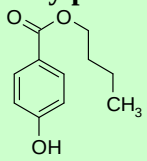
7.2. Environmental occurrence, fate, and effects of personal care products

7.2.1. Antibiotics

Relevant substances: mode of action and other properties

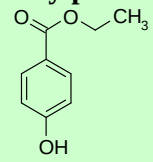
Parabens are extensively used as preservatives in topical antibiotic or corticosteroid preparations and in food and cosmetics to preserve skin creams and other such oil-containing products . Parabens are bactericides and since they all structurally resemble benzoic acid, they can be produced at a low cost. Parabens are allowed as food additives and have their own E-numbers: **methylparaben** (E218), **ethylparaben** (E214), and **propylparaben** (E216). No E-number exists for **butylparaben**.

Butylparabene



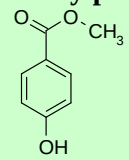
94-26-8
$C_{11}H_{14}O_3$, Mw=194.23
pKa=8.22, log D=3.43

Ethylparabene



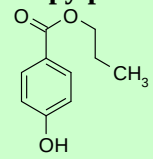
120-47-8
$C_9H_{10}O_3$, Mw=166.18
pKa=8.3, log D= 2.37

Methylparabene



99-76-3
$C_8H_8O_3$, Mw=152.15
pKa=8.3 , log D=1.84

Propylparabene



94-13-3
$C_{10}H_{12}O_3$, Mw=180.20
pKa=8.3, log D= 2.9

Results from previous screenings

Butylparaben has been detected in STP influent and effluent water, and sludge (Remberger, Woldegiorgis et al. 2005)

Ethylparaben (CAS 120-47-8) and **Propylparaben** (CAS 94-13-3) has been detected in STP influent and effluent water, and sludge (Remberger, Woldegiorgis et al. 2005), and high concentrations in cosmetic factory effluent, storm rain water overflow.

Methylparaben (CAS 99-76-3) was found in STP effluent water, and sludge (Remberger, Woldegiorgis et al. 2005), and in coastal water outside cosmetic factory, storm rain water overflow. A study performed by NIVA confirms ubiquitous detection of **Methyl**- and **Ethyl-parabens** in the Norwegian aquatic environment (Langford, unpublished data)

Relevant environmental properties, ERA, and monitoring recommendations

The use of parabens is believed to increase in Sweden. Parabens are or has been considered safe, but some (controversial) investigations have related parabens to allergic reactions, estrogenic activity, and even breast cancer, thus raising the concern regarding the use of these compounds. The parabens should therefore be included in future monitoring programs.

An estimated BCF of 110 suggests the potential for bioconcentration in aquatic organisms is high. Parabens are not expected to undergo hydrolysis in the environment. A log Kow of

3.57 also suggests the potential for bioconcentration in aquatic organisms is high. Biodegradation of **Methylparaben**, which degraded 100% after 6 days in sludge with an acclimation period of 2 days using a Zahn-Wellens test, suggests that biodegradation may be an important environmental fate process in water. Butylparaben was estrogenic at 10 mg/kg body weight (NIH 2007). In the ERA ranking, the parabens were ranked as follows: **Butylparaben** 21st, **Ethylparaben** 22nd, Propyl paraben 23rd, and **Methyl paraben** 25th. Parabens, in particular **Butylparaben**, is recommended for further monitoring.

Analytical strategy

Parabens are isolated by SPE and further analysed by GC-MS.

Triclosan

Relevant substances: mode of action and other properties

Triclosan is widely used as antibacterial agent in various industrial products, such as textile goods, soap, shampoo, liquid toothpaste and cosmetics. Triclosan is bacteriostatic and acts presumably by inhibiting fatty acid synthesis.

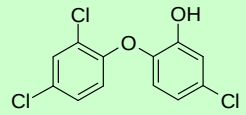
Results from previous screenings

Triclosan has been detected in STP influent and effluent water (Weigel, Berger et al. 2004; Møskeland 2006), sludge and sediment, but not in sea water (Weigel, Berger et al. 2004). In a Swedish study, **Triclosan** was even detected in biota (Remberger, Woldegiorgis et al. 2005).

Relevant environmental properties, ERA, and monitoring recommendations

There are several ecotoxicological studies of **Triclosan**. The hatchability and time to hatching in fertilized eggs exposed to 313 µg/L **Triclosan** for 14 days were significantly decreased and delayed, respectively in medaka (*Oryzias latipes*). Water solubility of **Triclosan** is 10 mg/L, and **Triclosan** is expected to adsorb to suspended solids and sediment. pKa of **Triclosan** is 7.9. A log Kow of 4.76 and a BCF range of 2.7 to 90 suggests that the potential for bioconcentration in aquatic organisms is low to moderate. A direct photolysis half-life of 10 days was measured in the Greifensee lake water, Switzerland under laboratory conditions (NIH 2007). The use of **Triclosan** has been stable or decreased during the last years. It is a substance that is used for its bactericidal properties in hygienic and cleaning products. In other products like sportswear of different kinds, **Triclosan** is used to prevent bad smell. Antibiotic resistence development is a problem with all antibiotics. Almost 3 tonnes is used in Swedish industry annually and in Norway 1.5 tonnes. **Triclosan** is ranked 3rd in the ERA conducted in the present study and should be further monitored.

Triclosan



3380-34-5
$C_{12}H_7Cl_3O_2$, Mw=289.5
pKa=7.8, log D=5.11

Analytical strategy

Triclosan is isolated from water by SPE and further analysed either by LC-MS or derivatisation prior to GC-MS.

7.2.2. Conservatives

Relevant substances: mode of action and pharmacokinetics

Butylated hydroxyanisole (BHA) and **Butylated hydroxytoluene** (**BHT**) is employed in food, cosmetics and pharmaceuticals to retard oxidative degradation of oils and fats. Oxygen reacts preferentially with the fat-soluble **BHA** or **BHT** rather than oxidizing fats or oils, thereby protecting them from spoilage.

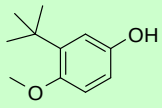
Results from previous screenings

BHA was detected in STP (Møskeland 2006). **BHT** has been detected in leachates, STP effluent, and biota (Fjeld, Schlabach et al. 2005).

Relevant environmental properties, ERA, and monitoring recommendations

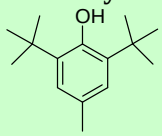
BHT has been banned for use in food in Sweden. In different studies, **BHT** has been reported to cure some cancers, but to encourage others. **BHT** is well studied because of public concern over synthetic preservatives. **BHT** was largely removed from food in the 1970s, to be replaced with the less well studied **BHA**. The environmental effects of **BHT** and **BHA** remain largely unknown. None of the compounds is included on the ERA ranking list constructed for the present study, and further monitoring seems not necessary.

BHA Butylated hydroxy anisole



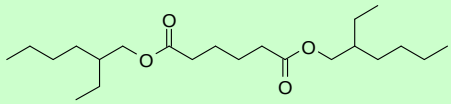
88-32-4
$C_{11}H_{16}O_2$, Mw=180.2
pKa=10.57, log D= 3.0

BHT Butylated hydroxy toluene



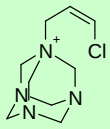
128-37-0
$C_{15}H_{24}O$, Mw=220.4
pKa=12.8, log D= 5.32

DEHA Diethylhexyl adipate



103-23-1
$C_{22}H_{42}O_4$, Mw= 370.6
pKa=n.a., log P= 8.1

Quaternium-15



51229-78-8
$C_9H_{16}ClN_4$, Mw=215,7
pKa= not found, log P/D=not found

Analytical strategy
Both compounds are isolated from water by SPE and subsequently analysed by GC-MS.

Adipates
Relevant substances: mode of action and other properties
Diethylhexyladipate (DEHA) is used as a plasticizer or solvent in the following cosmetics: bath oils, eye shadow, cologne, foundations, rouge, blusher, nail-polish remover, moisturizers and indoor tanning preparations.

Results from previous screenings
DEHA has been detected in STP and surface waters (Møskeland 2006).

Relevant environmental properties, ERA, and monitoring recommendations
With an estimated Koc value of 49,000, **DEHA** is expected to adsorb to suspended solids and sediment in water. Biodegradation test results indicate that **DEHA** is readily biodegradable. Therefore, the dominant degradation process in the aquatic environment is expected to be microbial degradation. No ecotoxicological data is available for **DEHA** (NIH 2007). No ERA ranking is obtained from this compound, and it may not be further monitored.

Analytical strategy
SPE followed by GC-MS is a promising analytical strategy.

7.2.3. Surfactants

Relevant substances: mode of action and other properties
Cocoamidopropyl betaine, CADG (CAS 86438-79-1) is a white to pale yellow solid substance that almost always is sold as a 30% aqueous solution. It contains one lipophilic part coming from the hydrocarbon chain of the coco fatty acid; the carbon chain length is between 8 and 18 carbon atoms, the C_{12} fatty acids being the most common, and a hydrophilic part consisting of the quaternary inner salt. The nitrogen in betaine is always quaternary, i.e. it is attached to four other atoms. That makes the substance act like a cationic surfactant in an acid solution, whereas it in an alkaline solution will not carry any net charge but continue to form its inner salt, it does not become a negatively charged ion. The substance is an amphoteric that thus does not act as zwitterions. The part carrying the charge consists of the amino acid glycine and the name betaine comes from the fact that trimethyl glycine was first extracted from sugar beets. The substance is a surface-active agent that is considered to be particularly mild to the skin and use has increased considerably in recent years. Half of all cocoamidopropyl betaine is used in cosmetic products like shampoo, shower gels, liquid soaps and a variety of similar hygiene products, particularly for children as they do not smart the eyes. The other half is used in different cleaners intended to be in contact with the skin, for instance hand washing-up products and liquids for contact lenses.

Results from previous screenings
To the best of our knowledge, CADG has not previously been subjected to environmental monitoring.

Relevant environmental properties, ERA, and monitoring recommendations
The extensive use by the industry makes it interesting to monitor this substance. In the conducted ERA ranking, it ended 2nd.

Analytical strategy
SPE followed by LC-MS.

Sodium lauryl ethersulphate
Relevant substances: mode of action and other properties
Sodium lauryl ethersulphate (CAS 3088-31-1) a colour- and odourless liquid with 35-60% of active ingredients. The substance is made from ethoxylated ether formed when a primary fat alcohol reacts with ethylene oxide. The ether is then sulphated with sulphuric acid. All alcohol is not ethoxylated, that means that ethoxylated dodecyl alcohol and sulphated sodium salt always will consist of a certain amount of sodium dodecyl sulphate. When choosing the amount of ethylene oxide that will react with the alcohol, different compounds are formed with different ability to form mixtures between water and non water-soluble substances. The substance-alkyl part dissolves in fat and the ethoxy part dissolves in water. The sulphate part makes the compound negatively charged and therefore the ethoxylated dodecyl alcohol and sulphated sodium salt belong to the anionic surfactant. The greatest quantity of dodecyl ethoxylated alcohol and sulphated sodium salt is used in cosmetics and hygiene products (shampoo and toothpaste). Other uses are as a detergent or as a degreaser.

Results from previous screenings
The compound is to our best knowledge not previously monitored.

Relevant environmental properties, ERA, and monitoring recommendations
The extensive use by Swedish industry makes it interesting to monitor this substance. According to the conducted ERA, it is ranked 4th, and should be monitored.

Analytical strategy
SPE followed by LC-MS.

Alkylphenols
Relevant substances: mode of action and other properties
Nonylphenol (CAS 25154-52-3) and **Octylphenol**. The main uses of nonylphenol are the production of nonylphenol ethoxylates and the production of resins plastics and stabilisers. Minor uses include the production of phenol oximes. The breakdown of nonylphenol ethoxylates in the environment may give rise to significant quantities of nonylphenol, therefore their use is considered in the risk assessment. The main use of nonylphenol ethoxylates is in products for industrial and institutional cleaning (30% total use). This is followed by use in emulsion polymerisation, as a textile auxiliary, captive use by the chemical industry, as a leather auxiliary, agricultural use, use in paints and other niche market uses.

Results from previous screenings
This compound is extensively detected in the environment (Moe, unpublished results).

Relevant environmental properties, ERA, and monitoring recommendations
Alkylphenols are weak to moderate estrogen mimetics, and should be further monitored. This is also supported by the ERA ranking, where **Nonylphenol** is ranked 8th and **Octylphenol** 14th.

Analytical strategy
Acetone extraction from solid samples, SPE from aqueous samples, both followed by LC-MS.

Quaternium-15
Relevant substances: mode of action and other properties
Quaternium-15 is by the industry and also in consumer products other than cosmetics.

Results from previous screenings
In a Norwegian study, the compound was claimed to be a target compound, however, no results regarding **Quaternium-15** was found in the report (Møskeland 2006).

Relevant environmental properties, ERA, and monitoring recommendations
Quaternium-15 has a K_{oc} value of 600 and an estimated BCF of 3.2, and is expected to adsorb to suspended solids and sediment. In the environment, the compound has an initial half-

life of about 1.5 days (NIH 2007). The compound ended un-ranked in the ERA conducted in the present work, and does not need future monitoring.

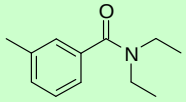
Analytical strategy
SPE followed by LC-MS.

7.2.4. Insect repellents

Relevant substances: mode of action and other properties
Diethyltoluamide (DEET) is an insect repellent especially effective against mosquitoes. DEET presumably acts by blocking the insect receptors for either CO_2 or lactate. Hence, the insect is blinded, and the desire to sting is also not triggered when this receptor is blocked.

Results from previous screenings
In Norway, **DEET** has been detected in STP effluent and sea water (Weigel, Berger et al. 2004).

DEET N,N-diethyl-m-Toluamide



134-62-3
C_{12} H_{17} N O, Mw= 191.3
pKa=na.a, log P= 1.96

Relevant environmental properties, ERA, and monitoring recommendations
Among the ecotoxicological data available, an LC_{50} of 110 mg/L over 96 hr for *Pimephales promelas* (fathead minnow) was reported. Due to a log Kow = 2.02, **DEET** is expected to adsorb to suspended solids and sediment. **DEET** has BCF values of 0.8-2.4, which suggests the potential for bioconcentration in aquatic organisms is low. **DEET**, at 100 mg/L, did not biodegrade under aerobic conditions over a period of 4 weeks with a sewage inoculums (NIH 2007). **DEET** should be considered implemented in future monitoring programs despite not ranked in the conducted ERA.

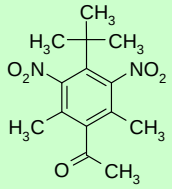
Analytical strategy
SPE followed by GC-MS.

7.2.5. Musks

Relevant substances: mode of action and other properties
Musks are used over a wide range of concentrations as fragrance in cosmetics, detergents, fabric softeners, household cleaning products and air fresheners. Nearly all musk fragrance used in perfumery today is synthetic. They can be divided into three major classes; aromatic nitro musks, polycyclic musk compounds, and macro cyclic musk compounds. The first two groups have broad uses in industry ranging from cosmetics to detergents. However, the detection of the first two chemical groups in human and environmental samples as well as their carcinogenic properties initiated a public debate on the use of these compounds and a ban or reduction of their use in many regions of the world. As an alternative, macro cyclic musk compounds are expected to replace them since these compounds appear to be safer.

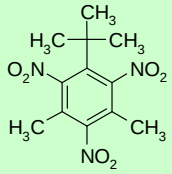
Results from previous screenings
Musks have also been detected in Norwegian air samples (Kallenborn, Gatermann et al. 1999). **Musk ketone** and **musk xylene** was detected in biota, STP effluent and sludge (Gatermann, Biselli et al. 2002). 2-amino musk ketone has been detected in biota, STP effluent, 2-amino musk xylene in biota, and 4-amino musk xylene in biota, STP effluent and sludge (Gatermann, Biselli et al. 2002). **Ethylene brassylate** was not detected in any matrix in a Norwegian study (Møskeland 2006). In a Norwegian-German collaboration, several musks were detected (Gatermann, Biselli et al. 2002; Gatermann, Biselli et al. 2002): **Galaxolide** in biota, STP effluent and sludge, **Phantolide** (AHDI) in biota, **Tonalide** (AHTN) in biota, STP effluent and sludge, and **Traseolide** (ATII) in biota.

Musk ketone



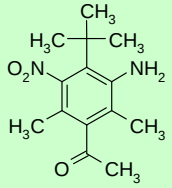
81-14-1
$C_{14}H_{18}N_2O_5$, Mw= 294.3
pKa=n.a., log P/D= 3.86

Musk xylene



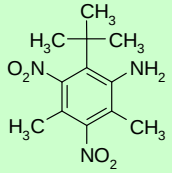
81-15-2
$C_{12}H_{15}N_3O_6$, Mw=297.3
pKa=n.a., log P/D=3.83

2-amino musk ketone



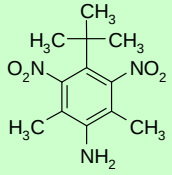
255393-52-3
$C_{14}H_{20}N_2O_3$, Mw= 264.3
pKa=n.a., log P/D= 3.83

2-amino musk xylene



107342-55-2
$C_{12}H_{17}N_3O_4$, Mw=267.3
pKa=n.a., log P/D= 4.35

4-amino musk xylene

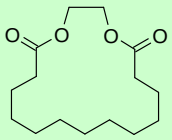


107342-55-6
$C_{12}H_{17}N_3O_4$, Mw=267.3
pKa=not found, log P/D= not found

Relevant environmental properties, ERA, and monitoring recommendations

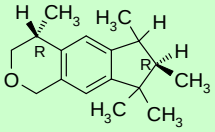
Tonalide was reported to affect the reproduction of *Daphnia magna*. **Tonalide** has a log Kow of 5.70 and in water, **Tonalide** is expected to adsorb to suspended solids and sediment. The BCF is 597-1069, suggesting that bioconcentration in aquatic organisms is high to very high. No oxidation of **Tonalide** occurred after 28 days using adapted industrial sludge with

Ethylene brassylate



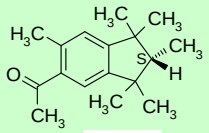
105-95-3
$C_{15}H_{26}O_4$, Mw= 270.4
pKa=n.a., log P=2.9

Galaxolide; HHCB

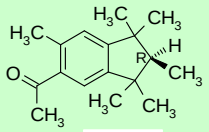


252332-96-0
$C_{18}H_{26}O$, Mw= 258.4
pKa=n.a., log P/D= not found

Phantolide; AHDI



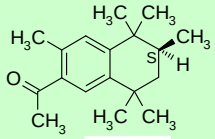
2S AHDI



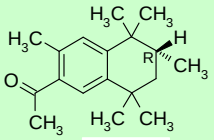
2R AHDI

15323-35-0
$C_{17}H_{24}O$ Mw=244.4
pKa=n.a., log P/D= not found

Tonalide; AHTN



3S AHTN



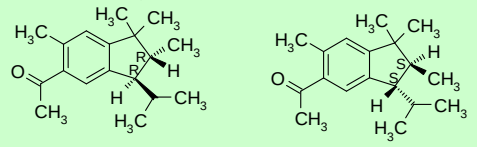
3R AHTN

21145-77-7
$C_{18}H_{26}O$, Mw= 258.4
pKa=n.a. , log P/D=not found

respirometric method. No CO_2 was released after 28 days using a sealed vessel with activated sludge adapted for 8 weeks or using sewage effluent and a modified Strum test after 28 days. Tonalide was degraded 80% in 3 weeks by the fungus *Aureobasidium pollutants* and was totally degraded in 6 days by *Phan-*

erochaete chrysosporium (NIH 2007).
The polycyclic musk compounds became popular after World War II and slowly supplanted the nitro-musks in popularity due to the latter's toxicity and molecular instability. However it was discover in the 1990's that polycyclic musks are also potentially harmful in that they can disrupt cellular metabolism and can potentially be mutagenic. Many of these musks were used in large quantities to scent laundry detergents. Commonly used polycyclic musks including **Galaxolide** and **Tonalide,** both ranked 19th in the present ERA, should be included in future monitoring programs.

Traseolide; ATII



2R 3R ATII

2S 3S ATII

68857-95-4
$C_{18}H_{26}O$, Mw= 258.4073
pKa=n.a., log P= 6.14

Analytical strategy
Musk are isolated from biota by column chromatography, followed by GC-MS.

7.2.6. Pigments

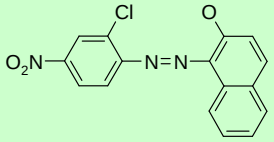
Relevant substances: mode of action and other properties
Pigments, such as C.I. 12085, are defined as non-soluble, which renders them to be susceptible to particle adsorption.

Results from previous screenings
The only pigment studied in Nordic countries C.I. 12085 was not detected in any of numerous matrices in a Norwegian study (Møskeland 2006).

Relevant environmental properties, ERA, and monitoring recommendations
C.I. 12085 is not recommended in future monitoring.

Analytical strategy
More method development must be done before pigment can be detected in the environment.

CI 12085



CAS 2814-77-9
$C_{16}H_{10}ClN_3O_3$, Mw=327.7
pKa=n.a., log P/D=5.25

7.2.7. Phthalates

Relevant substances: mode of action and other properties
Phthalates are used in a long range of different technical products as well as in personal care products. They behave like endocrine disruptors (Borch, Metzdorff et al. 2006) and are hence of environmental concern.

Results from previous screenings
Phthalates (e.g. **diethylhexyl phthalate; DEHP**) were detected in household dust (Moe 1998) and was part of a Norwegian screening study in 2006. In this study **DEHP** was detected in sediments, blue mussels, and fish (Bakke et al. 2007)

Relevant environmental properties, ERA, and monitoring recommendations
Diethylhexyl phthalate, DEHP (CAS 117-81-7) and **Dibutyl phthalate, DBP** (CAS 131-11-3) have been chosen for further monitoring. The substances are mainly used as a softeners in plastic products, hence the huge consumption. As plasticizer in plastic and rubber, the content of phthalates may be up to 40 per cent of the finished product. Particularly notable is the use of **DEHP** as a plasticizer in PVC plastic. Annually around 1 600 tonnes of the substance is used in Swedish industry (2005). **DEHP** is toxic to aquatic organisms is also believed to be reproductively harmful to humans. **DEHP** is ranked 1st, **DBP** 11th, **dimethyl phthalate** 13th, and **diethyl phthalate** 16th in the conducted ERA, thus, the phthalates should be further monitored.

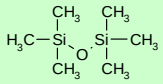
Analytical strategy
Following sample clean up, GC-MS is the preferred technique.

7.2.8. Siloxanes

Relevant substances: mode of action and other properties

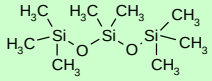
Siloxanes have widespread use in a variety of applications including food, soft drinks and cosmetics. Polydimethylsiloxanes (PDMS) is a group of polymers containing a silicon-oxygen skeleton. The size of the polymer is usually between 15 and 1,000 monomer units, which correspond to molecular weights of about 1,300 to 74,000. PDMS is a colourless liquid at room temperature. Siloxanes with only 2 to 6 silicon atoms (2 to 6 monomer units) can be both linear and cyclic molecules. They are solids or oily liquids and they are volatile. PDMS is manufactured by reaction between elementary silicon and methyl chloride followed by hydrolysis in water. The hydroxyl groups that are formed react. Both linear and cyclic oligomers are formed. These polymerise to linear silicon oils or to cross-linked silicon rubber. The properties of the end product depend on the monomers used as well as on the final chain lengths. Some small, often cyclic oligomers are isolated by distillation. Such oligomers, particularly octamethyltetrasiloxane is used to manufacture polymers where high purity and well-defined properties are required, e.g. for pharmaceuticals and cosmetics. PDMS is used in a number of applications as it has unique properties but also because it is a rather cheap raw material. PDMS is thermally stable, inert, resists water, ozone, UV- and gamma radiation, and has low surface tension and high surface activity. The low molecular cyclic siloxanes evaporate rapidly and are for that reason used as carriers/thinners for the heavier, more viscous siloxanes that are meant to remain on treated surfaces. In industry applications, PDMS is used as a lubricant (silicone oil), slips, hydraulic and transmission fluid. Other industrial uses are as a moisturizer and anti-foaming agent. An important application for PDMS is as a plasticizer in silicone joint sealants in the construction sector. In consumer products, PDMS is used e.g. on textiles and in polishes for its water repellent property and as an antifoaming agent in washing powder. Also in food, PDMS is used as an antifoaming agent in the production of beer, jam, juice, deep-frying fats and oils and as an anti-clotting agent in powdered food. Both PDMS and cyclic siloxanes, e.g. Octamethylcyclotetrasiloxane, are much used as softeners and emollients in cosmetics and skin care products. They are also used as anti-foaming agents in pharmaceuticals where they also may be the active ingredients. **Cyclic Siloxanes** have widespread use in a variety of applications including fermentation processes, instant coffee production, paper coatings and sizing, diet soft drinks, waste yeast tanks, food washing solutions, adhesives, textiles, deasphalting, boiler treatments, detergents, cleaning solutions, surfactants, cosmetic products, and polishes.

Hexamethyltrisiloxane



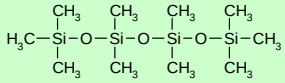
107-46-0
$C_6H_{18}OSi_2$, Mw=162.3818
pKa=n.a., log P= 4.2

Octamethyltetrasiloxane



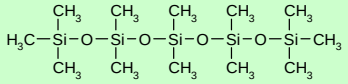
107-51-7
$C_8H_{24}O_2Si_3$, Mw=236.5373
pKa=n.a. log P=4.74

Decamethylpentasiloxane



141-62-8
$C_{10}H_{30}O_3Si_4$, Mw= 310.7
pKa= n.a., log P=6.52

Dodecamethylpentasiloxane



141-63-9
$C_{12}H_{36}O_4Si_5$, Mw= 384.8
pKa=n.a., log P/D= 8.31

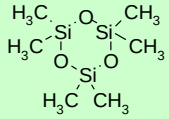
Results from previous screenings

Hexamethylcyclotrisiloxane (**D3**) has been detected in biota, **Octamethylcyclotetrasiloxane** (**D4**) in air, STP, coastal water, sludge (high), sediment and biota, **Decamethylcyclopentasiloxane** (**D5**) in air, STP, coastal water, sludge (high), sediment and biota, and **Dodecamethylcyclohexasiloxane** (**D6**) in air, STP, coastal water, sludge (high), sediment and biota (Kaj, Schlabach et al. 2005; Schlabach, Andersen et al. 2007).

In Norway and Sweden, some cyclic siloxanes have been detected in environmental samples

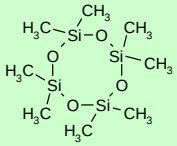
(Kaj, Schlabach et al. 2005; Schlabach, Andersen et al. 2007). **Hexamethyldisiloxane** (**MM**) was detected in air, STP, coastal water, sludge (high), sediment and biota, **Decamethyltetrasiloxane** (**MD2M**) in air, STP, sludge, coastal water, sludge (high), sediment and biota, **Dodecamethylpentasiloxane** (**MD3M**) in air, STP, coastal water, sludge (high), sediment and biota, and **Octamethyltrisiloxane** (**MDM**) in air, STP, coastal water, sludge (high), sediment and biota.

Hexamethylcyclotrisiloxane



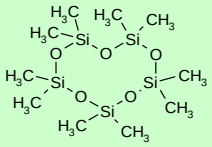
541-05-9
$C_6H_{18}O_3Si_3$, Mw=222.5
pKa=n.a., log P/D= not found

Octamethylcyclotetrasiloxane



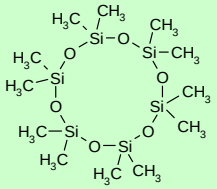
556-67-2
$C_8H_{24}O_4Si_4$, Mw= 296.6
pKa= n.a., log P/D= not found

Decamethylcyclopentasiloxane



541-02-6
$C_{10}H_{30}O_5Si_5$, Mw= 370.8
pKa= n.a., log P/D= not found

Dodecamethylcyclohexasiloxane



540-97-6
$C_{12}H_{36}O_6Si_6$, Mw=444.9
pKa=n.a. log P/D= not found

Relevant environmental properties, ERA, and monitoring recommendations

An LC_{50} of 10 µg/L over 14 days has been reported for *Oncorhynchus mykiss* (Rainbow trout). **D4** has a log Kow = 5.10 and a BCF of 12,400, suggesting that the potential for bioconcentration in aquatic organisms is very high. Poly-dimethylsiloxane (PDMS) fluids in intimate contact with many soils undergo siloxane redistribution and hydrolysis, resulting in the formation of low molecular weight cyclic and linear oligomers, as those described here (NIH 2007).

Octamethylcyclotetrasiloxane hydrolysed to dimethylsilanediol when treated with sewage sludge. As a member of this class biodegradation is not expected to be an important fate process. **Octamethylcyclotetrasiloxane** did not biodegrade when incubated with water/sediment under aerobic conditions (NIH 2007).

A LC50 for **Octamethyltrisiloxane** of 10 µg/L/14 days was reported for *Oncorhynchus mykiss*.

Due to a log Kow = 5.10, **Octamethylcyclotetrasiloxane** is expected to adsorb to suspended solids and sediment. Furthermore, a BCF of 12,400 suggests the potential for bioconcentration in aquatic organisms is very high.

Polydimethylsiloxane fluids undergo siloxane bond rearrangement to form low molecular weight linear and cyclic oligomers that are water soluble, indicating that soil mediated hydrolysis of **Decamethylcyclopentasiloxane** may be an important environmental process. **Octamethylcyclotetrasiloxane** hydrolysed to dimethylsilanediol when treated with sewage sludge. Dimethylsiloxanes in general are highly resistant to biodegradation (NIH 2007).

Siloxanes have also been identified in household dust (Moe 1998).

Octamethylcyclotetrasiloxane (CAS 556-67-2) and **Decamethylcyclotetrasiloxane** (CAS 541-02-6) have been chosen as candidates for further monitoring, ranking 9th and 12th, respectively, in the ERA conducted in the present study.

Analytical strategy

The siloxanes are analysed by GC-MS after sample clean up.

7.2.9. UV-filters

Relevant substances: mode of action and other properties

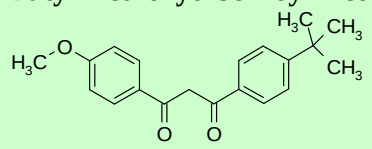
UV-filters or sunscreens are added to cosmetics to enable the user to sunbath over a potentially longer time without suffering sunburns.

Results from previous screenings

Only one report was found where **Butyl methoxydibenzoyl methane** (**Avobenzone**) was monitored (Møskeland 2006), however, the compound was not detected in any matrices.

A pilot screening study in 2006 by NIVA showed measurable concentrations in the environment sourced to discharges from STPs and release from bathers during the summer period. The sunscreens **benzophenone-3** (CAS 131-57-7), **ethylhexyl methoxy cinnamate** (CAS 5466-77-3), **octocrylene** (CAS 6197-30-4) and **4-methylbenzylidene** (CAS 36861-47-9) were all ubiquitously detected in Oslo fjord near bathing areas and WTP discharge points during summer. Trace levels of all targeted substances were also detected in winter suggesting that these seasonally used chemicals are relatively persistent.

Butyl methoxydibenzoyl methane



70356-09-1
$C_{20}H_{22}O_3$ Mw= 310.4
pKa=9.74 , log D=4.8

Relevant environmental properties, ERA, and monitoring recommendations

Avobenzone has an estimated Koc value of 1700, which indicates that **Avobenzone** is expected to adsorb to suspended solids and sediment. A BCF of 85 suggests the potential for bioconcentration in aquatic organisms is moderate, provided the compound is not metabolised by the organism.

Avobenzone is regarded as not easily degradable and potentially bio accumulative (NIH 2007).

No risk characterisation was performed for sunscreens, however, studies from Switzerland have shown that sunscreens bioaccumulate in fish (Buser et al., 2006) whilst 4-methylbenzylidene is also a known endocrine disrupter. Avobenzone and 4-methylbenzylidene is recommended for further monitoring.

Analytical strategy

LC-MS analysis after sample clean up.

Zinc pyrithione

Relevant substances: mode of action and other properties

Zinc pyrithione (CAS 13463-41-7) has a high PEC/PNEC risk quotient based on the data presented in Table 17.

Results from previous screenings

The only screening study for zinc pyrithione worldwide was performed in Sweden, on behalf of the Swedish EPA, in 2007 by IVL in collaboration with NIVA (Woldegiorgis A 2007). This study showed ZPT to occur in hospital effluent and WTP influent (2 – 32 µg/L) but not effluent.

Relevant environmental properties, ERA, and monitoring recommendations

ZPT has a reported $t_{½}$ of < 1 h mainly degrading through photolysis. However a recent study performed by NIVA shows that the laboratory photolysis of ZPT does not represent what occurs in the environment and that at 1m depth in Oslo fjord the $t_{½}$ increases to 50 h with little or no degradation occurring at low light conditions below 20 m (Thomas et al., In press). These data suggest that although the Swedish screening study showed zinc pyrithione not to occur in WTP effluents and surface waters it did occur in hospital effluents and sludge suggesting that accumulation is possible in low light environments. The high risk quotient, sparse occurrence data, dependency on light for degradation suggests that zinc pyrithione warrants further attention with samples being collected from low light environments which may receive direct inputs of untreated wastewater (i.e. Northern latitude cities during winter).

7.2.10. Concluding remarks on the monitoring data of personal care products

Triclosan, musks, siloxanes, and phthalates have been widely detected in the Nordic countries, and it is recommended that these compounds be implemented in future monitoring programs. Sun-blockers/UV-filters are not widely monitored throughout the Nordic envi-

ronment, but these compounds should also be included in future programs.

7.3. Prioritisation for further monitoring

Out of the table of cosmetic ingredients the following substances has been selected based on our current knowledge (The Swedish Chemicals Inspectorate, Kemi, www.kemi.se) on their toxicity and persistence.

Table 17: Estimated risk quotients for Personal care products (PCPs) prioritised for further monitoring in Sweden based upon 2006 consumption data or measured environmental concentrations (MEC) and measured PNECs.

Rank	Substance	Estimated Release, [kg/year]	CAS	PEC Sweden [µg/l]	MEC [µg/l]	PNEC [µg/l]	PEC/ PNEC
1	Diethylhexyl phthalate[1]	1611000	117-81-7	241.7		0.0025	96660
2	Cocoamidopropyl betaine (CADG)[1]	236400	86438-79-1	35.5		0.02	1773
3	Triclosan[1]	2760	3380-34-5	0.41		0.0005	828
4	Sodium lauryl ethersulphate[1]	3752400	3088-31-1	562.9		1	563
5	Cetrimonium salts[1]	24000	57-09-0	3.6		0.01	360
6	Resorcinol[2]	648000	108-46-3	97.2		0.9	108
7	Cocamide DEA[1]	228000	61789-19-3	34.2		0.32	107
8	Nonylphenol[1]	10000	25154-52-3	1.5	0.46	0.017	88
9	Octamethylcyclotetrasiloxane[1]	5000	556-67-2	0.8		0.034	22
10	Sodium laurylsulphate[1]	1990000	151-21-3	298.5		20	15
11	Dibutyl phthalate[2]	210000	84-74-2	31.5		2.2	14
12	Decamethylcyclotetrasiloxane[1]	19000	541-02-6	2.9		0.21	14
13	Dimethyl phthalate[2]	400000	131-11-3	60		9.6	6.3
14	Octylphenol[1]	MEC data	67554-50-1	n/a	0.036	0.03	1.2
15	Butyl methoxydibenzoyl methane[2]	10000	70356-09-1	1.5		1.97	0.76
16	Diethyl phthalate[2]	15000	84-66-2	2.3		3.65	0.62
17	EDTA[2]	14000	60-00-4	2.1		9	0.23
18	Octamethyltrisiloxane[1]	<100	107-51-7	0.02		0.28	0.05
19	Galaxolide[1]	1000	1222-05-5	0.2	0.042	0.59	0.25
19	Tonalide[1]	< 100	1506-02-1	0.02	0.010	0.35	0.04
20	Hexamethyldisiloxane[1]	<100	107-46-0	0.02		0.62	0.02
21	Butylparaben[1]	MEC data	94-26-8	n/a	0.001	0.404	0.002
22	Ethylparaben[1]	MEC data	120-47-8	n/a	0.001	1.15	0.0009
23	Propylparaben[1]	MEC data	94-13-3	n/a	0.003	5	0.0006
24	Celestolide[2]	MEC data	13171-00-1	n/a	0.0008	1.6	0.0005
25	Methylparaben[1]	MEC data	99-76-3	n/a	0.0018	10	0.00018
26	Musk ketone[1]	MEC data	81-14-1	n/a	< 0.0001	1.32	7.58E-05
28	Bronopol[2]	1080	52-51-7	0.16	n.d.	0.4	0.405
29	Zinc pyrithione[2]	5000	13463-41-7	0.75	n.d.	0.012	63

[1]: Frequently measured in the Nordic environment.
[2]: Occasionally measured in the Nordic environment.
[1]: Seldom or never measured in the Nordic environment.

7.4. Sampling strategy and analytical methods

Personal care products will predominantly enter the environment via WTW effluent, although certain seasonally used products, such as sunscreens and insect repellents, can also enter the environment via direct release following bathing. It is therefore recommended that the screening of personal care products is performed in WTW final effluent to estimate inputs into the environment and in the receiving water body. If sunscreens and insect repellents, which are known to occur in Norwegian coastal waters (Langford and Thomas, Unpublished data) are to be included then it is recommended that bathing areas are included during the summer period in addition to a transect moving away from the point of WTW effluent discharge. Effluents from manufacturing plants should be included in future monitoring programs.

Analytical possibilities

For most of the substances prioritised analytical techniques have been published and are available.

8. Narcotics

8.1. Introduction

In Norway, there has of late been increased media attention concerning the escalating use of illicit drugs, in particular cocaine, within society. However, accurate estimations of community drug abuse are difficult to produce and current methods for the estimation of illicit drug use within society often suffer from significant shortcomings. Estimating the amount of these substances entering the environment is therefore difficult. The first report concerning the presence of illicit materials in treated wastewater appeared in 2004, whereby low ng/L of **methamphetamine** and **3,4-methylenedioxy methamphetamine** (MDMA or 'ecstasy') were individually detected in the effluent of two monitored wastewater treatment plants in Nevada and South Carolina in the United States, respectively. Although no further research was conducted in this instance, it was acknowledged that the detection of these two illicit drugs corroborated evidence from the United States Drug Enforcement Agency (USDEA) that both chemicals were becoming increasingly problematic in the metropolitan areas surrounding the sampled plants. More recently amphetamine was also detected in sewage sludge by Austrian researchers in the low µg/kg range, however, caution must be used when interpreting such results as amphetamine and similar compounds may also be presented in wastewater treatment plants as metabolites of prescription drugs used in the treatment of Parkinson's disease. Additional data to support the occurrence of narcotics in the environment was performed by Italian researchers in 2005 where levels of **cocaine** and its primary metabolite, **benzoylecognine**, were detected in surface waters and treated effluent (Zucatto *et al. 2005).* More recently, a study has emerged where the levels of a broad suite of illicit drugs were determined using isotope dilution LC-ESI-MS/MS in the treated effluents of wastewater treatment plants in Milan, Italy and Lugano, Switzerland. In both plants the majority of the target analytes were detected in the influent samples, while reduced quantities were detected in the treated effluent, suggesting the existence of removal mechanisms with in the treatment plant. More recently comparative data have been reported for Oslo and Dublin, which show similar levels of occurrence in two of Europe's capital cities (Bones et al., 2007). As far as we are aware there are no other reported data on the occurrence of narcotics in the Nordic environment.

8.2. Environmental occurrence, fate, and effects of narcotics

There has only been conducted one analysis for narcotics in Norway, and these results are not yet published. However, narcotics have been monitored in the EU, and among others, **Cocaine**, **THC**, and **Amphetamine** was detected (Bones, Thomas et al. 2007).
The narcotics most used in Norway are Cannabis (active compound **tetra-hydro cannabinol; THC**), **Amphetamine**, Benzodiazepines (e.g. **Flunitrazepam**), **Heroin**, and **Cocaine**. Benzodiazepines are used along with narcotics to enhance the effect of the latter. The environmental effects of illicit drugs are debated.

Other narcotics, such as **Ecstasy** (N-Methyl-3,4-methylenedioxy-amphetamine), **Methamphetamine**, **Opium**, **LSD** (Lysergide), **GHB** (gamma-Hydroxybutyrate), and **Qat** are presumably used by a lesser extent, and are not further discussed in this section. Qat is in the perspective of environmental risk assessment a rather obscure narcotic drug primarily consumed by some minor ethnic groups in Sweden. Annually the Swedish customs seize some 6.5 tonnes and the police some 200 kg. However, despite the large amounts possibly released into the environment from abuse of this drug (perhaps as much as 60-70 tonnes annually) it is not considered to be of environmental concern. The active narcotic substances of the Qat plant, Cathionine and Cathine, constitute only a small fraction plant weight and have the propensity of a very fast biodegradation (the herbs needs to be consumed by the user within 2 days after harvest to induce any effect).

Regarding seized illegal substances in Sweden, there is also a large quantity of the pharmaceutical **Flunitrazepam** ("Rohypnol"), corresponding to 436,250 tablets (0.5-1 mg/tablet) or 0.5 kg active substance seized. This would correspond to an annual estimated release of 5-50 kg. If this figure is compared with the annually reported prescribed sales of legal flunitrazepam (10.4 kg in 2006), it is obvious that illegal smuggling is at least of the same order of magnitude as the legal sales.

Narcotics and illicit drugs have not been systematically monitored in the Nordic environment. As some of these compounds are readily metabolised, a monitoring programme for narcotics must include their metabolites.

8.3. Prioritisation for further monitoring

The PECs are estimated the same way as the pharmaceuticals, and are corrected for metabolism in the table. Data on narcotics prevalence reported to *Monitoring Centre for Drugs and Drug Addiction* (EMCDDA) are rather limited in Sweden compared to Norway. Extensive amounts of data and statistics have been collected in Sweden over 3-4 decades. However, it is rather difficult, and sometimes also controversial, to transform seizure statistics, hepatite c- and HIV incidence, attitude investigations amongst teenagers and army recruits, to the actual consumption in kilograms of pure substance subsequently released into the Swedish environment. The uncertainties accompanying such estimates are significant, to say the least.

It is generally accepted that drug prevalence is very low in Sweden in comparison with other European countries. The drug prevalence is amongst the lowest recorded in Europe over time (personal communication, U. Guttormsson, Centralförbundet för alkohol- och narkotikaupplysning, CAN). In an attempt to estimate annual consumption of narcotic substances in Sweden an assumption was made that the overall drug prevalence is lower in Sweden than in Norway. Whether this assumption is completely true for all types of narcotics is however elusive.

Table 18: Calculation of narcotic PECs for Norway based on 2006 data.

Drug	Prevalence of use (%)	Number of users	Average quantity used	Typical dose (g)	Purity (2006)	Estimated use (kg/year)	PEC (µg/L)
Cannabis	4.6	137,658	0.7 (grams THC/day)			35,172	10.29
Opiates	0.4	11,970	2.09 (grams/day)	0.25	0.29	662	0.19
Amphetamine	1.1	32,918	9.71 (points/day)	0.1	0.43	4.871	1.43
Cocaine	0.8	23,940	3.17 (hits/day)	0.1	0.38	1,053	0.31
Ecstasy	0.5	14,963	1.47 (tablets/day)	0.1	1	803	0.23

These compounds were seldom or never measured in the Nordic environment.

Table 19: Comparison of narcotic PECs with MECs for Oslo, Norway

Drug	Metabolite	PEC (µg/L)	MEC (µg/L)
Cannabis (THC)	Tetrahydrocannabinol (30%)	3.1	
	11-nor-9-carboxy-THC (THC-acid) (70%)	7.2	
Opiates (Heroin)	Morphine (42%)	0.08	
Amphetamine	Amphetamine (30-74% unchanged)	0.33-0.80	
Methamphetamine	Methamphetamine (43% unchanged)	0.15	
Cocaine	Cocaine (10%)	0.03	0.15
	Benzoylecognine (90%)	0.28	0.02
Ecstasy (MDMA)	MDMA (65% unchanged)	0.15	

These compounds were seldom or never measured in the Nordic environment.

Table 20: Calculation of narcotic PECs for Sweden and ECOSAR modelled PNEC data.

Ranking	Drug	Estim. release [kg/year]	CAS	PEC [µg/l]	PNEC [µg/L] (ECOSAR)	PEC/ PNEC	PEC(Met)/ PNEC[a]
1	Cannabis	45990	(1972-08-3,THC)	6.9	0.016	431	86-201[b]
2	Amphetamine	6659	300-62-9	1	3.80	0.26	0.13[c]
3	Heroin	1244	561-27-3	0.19	9.83	0.02	0.005[d]
4	Cocaine	3167	50-36-2	0.48	4.91	0.01	0.006[e]
5	Ecstasy (MDMA)	1449	42542-10-9	0.22	2.70	0.01	0.035[f]
6	Methampheta-mine	1500	537-46-2	0.23	2.26	0.1	0.043[g]
7	Opium	500	(57-27-2, morphine)	0.08	32.43	0.002	n/a
8	LSD (Lysergide)	800	50-37-3	0.12	4.63	0.03	n/a

These compounds were seldom or never measured in the Nordic environment.

Drug prevalence was arbitrarily set to a lower number than the corresponding reported Norwegian value (for instance 2 % of the Swedish population were assumed to use cannabis at averaged Norwegian daily doses corresponding to 0.7 grams of THC/day). The calculation using that prevalence proceeded in an "estimated release (kg/year)". If that estimated release number corresponded to 10-100 times the mass of cannabis seized by Swedish police and customs, the estimated prevalence seemed ok. Otherwise, prevalence data were iteratively changed as to yield estimated release data meeting the requirement that seized amounts should correspond to 1-10 % of the totally released amount while prevalence in Sweden would always be lower than the corresponding value of Norway.

In case of specific drugs where no Norwegian data were available, it was assumed that seized amounts by Swedish customs and Police corresponded to 1-10 % of the estimated release (methamphetamine, Qat and Opium). Methamphetamine prevalence was set to be slightly lower than the calculated amphetamine prevalence while opium prevalence was arbitrarily set to 0.02 %, giving an estimated release corresponding to 12 times the seized amount. From the data presented in Table 18 and

Table 19, it is predicted that concentrations of most narcotics are greater than 0.01 µg/L and the sparse MEC data available for Oslo confirm this. PECs generated for both Norway and Sweden have been calculated from data that carries a high degree of uncertainty. This is confirmed by comparing the MEC for cocaine with the concentrations measured in Oslo. The PEC accounts for only 20% of the MEC. It is therefore reasonable to expect that the narcotic PECs significantly underestimate the amounts of narcotic substances entering the environment. Data from screening studies in Italy, Germany, Ireland, Norway and the UK show that narcotic substances occur in WTP effluents and receiving surface waters (Zucatto et al., 2005; Bones et al., 2007).

Further analyses of these data are particularly difficult since there are no published aquatic ecotoxicological data for narcotic substances. ECOSAR modelling provides acute $PNEC_{ECOSAR}$ data but with a very high degree of uncertainty. In addition to this uncertainty one must consider whether traditional approaches to extrapolating chronic PNECs are at all relevant when considering narcotic substances. As described above the acute/chronic ratio (ACR) approach is coming under increased scrutiny when considering drugs since the approach is founded on the toxic mechanism of non-specific narcosis, which is by definition not applicable to narcotics, which have a very specific effect. A high degree of uncertainty is therefore associated with the modelled acute PNEC and any assumptions made in terms of extrapolating chronic PNEC data.

Using the precautionary principle the high degree of uncertainty associated with the estimation of PEC, calculation of PNEC (using ECOSAR) and extrapolation of chronic PNEC suggest that the further evaluation of the following narcotics is performed:

- **Cannabis**
- **Opiates**
- **Amphetamine**
- **Methamphetamine**
- **Cocaine**
- **Ecstasy**

This is supported by the occurrence of these substances in other European screening studies.

8.4. Sampling strategy and analytical methods

Narcotic substances are similar to human pharmaceuticals and many personal care products as they enter the environment primarily through WTW. It is recommended that the collection of samples for narcotics is focused on WTW final effluent and receiving water bodies. Importantly, different narcotics have different patterns of use; e.g. cocaine is mainly a social drug used at weekends, whilst heroin use is more uniform. Allowances therefore need to be made for this when designing a sampling programme. For narcotic screening it is recommended that daily composites effluent samples are collected over a one week period (including weekend) with receiving water samples collected on a single occasion.

Analytical possibilities

Analytical techniques based on extraction by solid phase extraction and analysis by liquid chromatography coupled to mass spectrometry (Zucatto et al., 2005; Bones et al., 2007).

Table 21: Summary describing sampling scenarios to be considered

	HP	PCP	Narcotics	VP Land	VP Aquaculture
WTW influent					
WTW effluent					
WTW sludge					
Storm water overflow					
Hospitals					
Landfill sites					
Factories (pharma)					
Receiving waters					
Receiving Fields					
Farms					
Aquaculture facilities					

Key:

- Minimum sampling requirements
- Improved resolution
- Complete overall picture

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10. Appendices

10.1. Pharmaceuticals exempted from risk assessment in this study.

ATC-Code	Substances	Comment
A10A	Insulins and analogues	Polypeptides
A16AA	Amino acids/derivates	
A16A B02	Imiglucerase	Glycoprotein
A16A B04	Agalsidase beta	Glycoprotein
B01A B02	Antithrombin III	Protein
B01A C13	Abciximab	MAb
B01A D01	Streptokinase	Protein
B01A D02	Alteplase	Glycoprotein rtPA
B01A D07	Reteplase	rtPA
B01A D10	Drotrecogin Alfa	rhProteinC
B01A D11	Tenecteplase	r-glycoprotein
B01A D12	Protein C	human protein
B01A E04	Melagatran	Syntethic dipeptide
B01A E05	Ximelagatran	Dipeptide
B01A E06	Bivalirudin	Peptide
B02A A	Amino acids	
B02A B	Aprotinin	Proteinase inhibitors
B02B C10	Fibrinogen, human Fibrinogen	Protein
B02B C30	Tachosil	Fibrinogen and thrombin coated collagen
B02B D	Coagulation factors	
B03X A	Erythropoietin, Darbepoetine	r-glycoprotein
B05A A01	Albumin	h-protein
B05A A02	Octaplase	h-protein
B05B A01	Amino acids	
B05X B	Amino acids	
B06A A	Streptokinase, combinations	Enzymes
G03G A01	Chorionic gonadotrophin	protein
G03G A05	Follitropin Alfa	Peptide
G03G A06	Follitropin beta	Peptide
G03G A07	Lutropin Alfa	Protein
G03G A08	Choriogonadotropin Alfa	Protein
H01A A02	Tetracosactide	Synthetic polypeptide, 24 Amino acids
H01A C01	Somatropin	Polypeptide/protein
H01A X01	Pegvisomant rDNA	Polypeptide/protein
H01B A02	Desmopressin	Peptide
H01B B02	Oxytocin	Nano Peptide
H01C A01	Gonadoreline	Octa Protein
H01C A02	Nafareline	Deca Peptide
H01C B02	Oktreotide	Cyclic Octa peptide

ATC-Code	Substances	Comment
H01C B03	Lanreotid	Cyclic Octa peptide
H01C C01	Ganerelix	Deca Peptide
H01C C02	Cetorelix	Deca Peptide
H04A A01	Glucagon	Polypeptide (29 amino acids)
H05A A02	Teriparatide	34 amino acids N- terminal of rhPTH
J01X A01	Vancomycin	Tri cyclic glyco-peptide
J01X A02	Targocide	Tri cyclic glyco peptide
J05A X07	Enfurvitide	Polypeptide
J06	Immunoglubuline	Protein
J07A H07	Meningitec,	oligosaccharide conjugated protein
J07A L02	Prenevar	saccharine conjugated to a protein
J07B C	Engerix B	Hepatit B virus antigen, protein
L01X C	Monoclonal antibodies	Protein
L01X X02	Asparaginas	Protein
L02A E01	Buserelin	Peptide
L02A E02	Leoprorelin	Nano Peptide
L02A E04	Tripeptorelin	Peptide
L03A A02	Filgrastim	Glycoprotein
L03A A10	Lenograstim	Glycoprotein
L03A A13	PEG-filgrastim	PEG G-CSF
L03A B	Interferones	Protein
L03A X11	Tasonermin	Protein
L03A X13	Glatirameracetat	4 amino acids
L04A A02	Muromonab	MAb
L04A A04	ATG	Horse MAb against human ATG
L04A A08	Daclizumab	MAb
L04A A09	Basiliximab	MAb
L04A A11	Etanercept	Glycoprotein
L04A A12	Infliximab	MAb
L04A A14	Anakinra	Interleukin 153 amino acids
L04A A17	Adalimumab	MAb
L04A A21	Efalizumab	MAb
M05B C01	Dibotermin alfa	Protein
R05C B01	Acetylcysteine	Amino acid
R05C B13	Dnase	Glycoprotein
V03A F07	Rasburikas	Protein
V03A F08	Palifermin	Protein
V06D D	Amino acids	
V06 CA00	Amino acids	

Other excluded substances accordingly;
Electrolytes (inorganic salts such as NaCl), naturally occurring vitamins such as cyanocobalamine (vitamin B12), laxatives (such as ispaghula), industrial chemicals (such as polyethylene glycol, ethylene glycol, rubber, paraffin, silicones, saccharose, fructose, ricinic oil), and oligomeric substances with an undefined molecular weight or molecular weights exceeding 800 Da (such as *Saccharomyces boulardii*, Rifampicine, Colestyramine, colestipole, and acarbose).

10.2. Proposed future monitoring in Europe

The project team sent a questionnaire to all known contact persons in the Nordic Countries and EU asking for information about planned or ongoing monitoring or screening activities of PPCPs including compounds and matrices included, duration of the study, and the funding institution. The detailed answers are listed in the table below

Country	UK
Targeted compounds	Trimethoprim, Diclofenac, Sulfamethoxazole and acetyl metabolite, Paracetamol, Mefenamic acid, ibuprofen, erythromycin, Dextropropoxyphene, lofepramine, Tamoxifen, Propranolol
Period	2002
Matrices	Sewage effluent
Responsible Agency	UK Environment Agency
Contact	tatiana.boucard@environment-agency.gov.uk
Reference/abstract	http://publications.environment-agency.gov.uk/pdf/SP6012-06-TR-e-p.pdf

Country	UK
Targeted compounds	ciprofloxacin, Doramectin, Enrofloxacin, Ivermectin, Lincomycin, Oxytetracycline, sulfadiazine, and Trimethoprim
Period	2004
Matrices	soil, surface water, sediments
Responsible Agency	UK Environment Agency
Contact	tatiana.boucard@environment-agency.gov.uk
Reference/abstract	http://publications.environment-agency.gov.uk/pdf/SCHO0806BLHH-e-e.pdf http://publications.environment-agency.gov.uk/pdf/SP6012-06-TR-e-p.pdf

Country	UK
Targeted compounds	Over 50 compounds: basic, neutral and acidic pharmaceuticals, personal care products and illicit drugs
Period	2005-2007
Matrices	Surface water and wastewater (influent and effluent)
Responsible Agency	EU
Contact	B.Kasprzyk-Hordern@hud.ac.uk
Reference/abstract	The aim of the Marie Curie TOK Fellowship in Analytical Environmental Toxicology was to establish analytical procedures and to verify the presence and fate of PPCPs in the aqueous environment. A new technique, ultra performance liquid chromatography – positive/negative electrospray tandem mass spectrometry (UPLC-ESI/MS/MS) was utilised for the analysis of multiple classes of pharmaceuticals and their metabolites (acidic, basic and neutral compounds: analgesic/anti-inflammatory drugs, antibiotics, antiepileptics, beta-adrenoceptor blocking drugs, lipid regulating agents, etc.), illicit drugs (amphetamine, cocaine and benzoylecognine) and personal care products (sunscreen agents, preservatives, disinfectant/antiseptics) in surface water. Over 50 compounds were analysed with new simultaneous multi-residue methods. The overall project allowed for an estimation of the risk associated with the presence of PPCPs in the aqueous environment in South Wales. Two rivers: River Taff and River Ely (South Wales) and two wastewater plants discharging treated wastewater effluent into these rivers were the subject of investigation over a period of 10 months. Several pharmaceuticals and personal care products were determined in river water at levels ranging from sin-

	gle ng L-1 to single µg L-1. Among the most common PPCPs were: Paracetamol, Atenolol, sulfasalazine, sulfapyridine, codeine, gabapentin, Tramadol, Carbamazepine, aspirin, salicylic acid, Furosemide, Ketoprofen, naproxen, valsartan, Diclofenac and ibuprofen.
Country	Eire
Targeted compounds	acetaminophen, salicylic acid, Propranolol, clofibric acid, Ketoprofen, Diclofenac sodium salt, bezafibrate, Warfarin, flurbiprofen, indomethacin, Ivermectin, erythromycin, Oxytetracycline, ibuprofen, meclofenamic acid, gemfibrozil, Atenolol, salbutamol, Sulfamethoxazole, Sulfamethazine sodium salt, Furosemide, pravastatin, Carbamazepine, nimesulide, Metoprolol, Clotrimazole, Trimethoprim, caffeine, naproxen, Triclosan
Period	Ongoing
Matrices	Sewage sludge and soils
Responsible Agency	Environmental Protection Agency (Ireland)
Contact	B.paul@dcu.ie
Reference/abstract	An analytical method to simultaneously determine a selection of 27 frequently prescribed and consumed pharmaceuticals in biosolid enriched soils and digested sludge was developed, including Analgetics, veterinary and human antibiotics, anti-inflammatories, anti-coagulants, anti-diabetics, psychiatrics, lipid regulators, beta-blockers and stimulants. Using a combination of pressurized liquid extraction, solid phase extraction and liquid chromatography with tandem mass spectrometry, it was possible to detect all analytes in each sample type at the low-sub ng/g level. Current work involves adsorption kinetics for the selected pharmaceuticals to soils and sludge.
Country	Eire
Targeted compounds	Cocaine hydrochloride, morphine sulphate salt pentahydrate, methadone hydrochloride, ketamine hydrochloride, heroin and Ä9-tetrahydrocannabinol, (Ä9-THC), benzoylecognine hydrate, cocaethylene, D-amphetamine sulphate salt, temazepam, diazepam, Carbamazepine, Fluoxetine hydrochloride, lysergic acid, diethylamide (LSD), papaverine hydrochloride, 3,4-methylenedioxymethamphetamine, hydrochloride (MDMA) and 2-ethylidine-1,5dimethyl-3,3-diphenylpyrrolidine, perchlorate (EDDP)
Period	ongoing
Matrices	wastewater, biological material
Responsible Agency	IRCSET - Irish research council for science engineering and technology
Contact	B.paul@dcu.ie
Reference/abstract	
Country	Sweden
Targeted compounds	Antibiotics: Ofloxacin (fluoroquinolone), Norfloxacin (fluoroquinolone), Ciprofloxacin (fluoroquinolone)
Period	Annual
Matrices	Sewage sludge
Responsible Agency	Swedish EPA
Contact	Peter.Haglund@chem.umu.se
Reference/abstract	

Country	Sweden
Targeted compounds	Initially all human pharmaceuticals currently available on the Swedish market. Detailed studies of a smaller selection of these (approx 50). Final selection of compounds will be made during the programme period.
Period	**-2011**
Matrices	Water, blood plasma
Responsible Agency	Swedish Foundation for Strategic Environmental Research (Mistra)
Contact	cr@infra.kth.se
Reference/abstract	MistraPharma will initially consider all 1200 APIs currently available on the Swedish market. To make this feasible, a transparent and systematic risk ranking of APIs will be performed and refined stepwise. One of the criteria for selecting APIs for in-depth toxicity tests will be modelled and/or actual data on bioconcentration of drugs in fish exposed to sewage effluents and a comparison with human/experimental animal therapeutic plasma levels. The ecotoxicity of the prioritized APIs will be investigated primarily in fish and Daphnia, using both exploratory and more targeted tests. The prioritized APIs will also be used as model compounds in the evaluation of wastewater treatment technologies, and thus form the basis of the overall programme conclusions. The systematic generation of data within MistraPharma will enable an empirical investigation of the efficiency of different tests and combinations of test in identifying effects of concern. To facilitate statistical analyses the data generated within MistraPharma as well as relevant data from other projects will be gathered in a MistraPharma database.

Country	The Netherlands
Targeted compounds	Diclofenac Ibuprofen Ketoprofen, Indometacine Naproxen Fenoprofen, Phenazone dimethylaminophenazone propylphenazone, clofibric acid Bezafibrate Gemfibrozil, Etofibrate Fenofibrate fenofibric acid, Simvastatin, Iopamidol Iopromide Iomeprol, amidotrizoic acid Iodipamide Iohexol, iopanoic acid iotalamic acid Ioxaglic acid, ioxitalamic acid, Carbamazepine, Pentoxifylline, Diazepam, Metoprolol Propranolol Atenolol, Bisoprolol Sotalol Pindolol, Betaxolol, Salbutamol Clenbuterol Terbutaline, Cyclophosphamide Ifosfamide, Clarithromycin Erythromycin anhydro-erythromycin, Oleandomycin Roxithromycin Clindamycin, Spiramycin Tylosin Sulfadiazine, Sulfamerazine Sulfamethoxazole Sulfadimidine, Trimethoprim Chloroamphenicol Metronidazol, Ronidazol Furazolidone Dapsone, Virginiamycin Amoxicillin Ampicillin, penicillin G penicillin V Oxacillin, Nafcillin Cloxacillin Dicloxacillin, Ciprofloxacin Enoxacin Enrofloxacin, Norfloxacin Ofloxacin Chlorotetracycline, Doxycycline Meclocycline Oxytetracycline, Tetracycline
Period	Annual
Matrices	Effluent and surface waters
Responsible Agency	RIZA, RIWA
Contact	stoks@riwa.org
Reference/abstract	http://www.riwa.org/e_publikaties/116_farma_res.pdf

Country	Denmark
Targeted compounds	
Period	No ongoing monitoring
Matrices	
Responsible Agency	
Contact	
Reference/abstract	

Country	Finland
Targeted compounds	Carbamazepine, Diclofenac, naproxen, octatetracycline, ciprofloxacin, sulfadiazine and Metformin
Period	-2010
Matrices	water, sediments, aquatic organisms
Responsible Agency	Finnish Graduate School in Environmental Science and Technology
Contact	lkronber@abo.fi
Reference/abstract	To advance understanding to what degree biota in the boreal environment is exposed to and affected by the occurrence of commonly used pharmaceuticals in the aquatic environment. We aim at studying the environmental fate of a series of pharmaceuticals, including their partitioning, photo transformation, hydrolysis and biotransformation. The transformation products will be structurally determined and they will be used as the reference compounds for their determination in water and for studies dealing with aquatic toxicity. Study subjects: -to consider the role of major factors in the boreal environmental – solar UV, humic substances, brackish water, and temperature as modifying factors affecting the environmental fate (i.e. stability / transformation, transportation) and ecotoxicological impacts of pharmaceuticals -structural determination of transformation products, rate constants for transformation reactions, their stability, aquatic toxicity – including reciprocity of effects - of stable transformation products -partitioning between solids and water -lakes, rivers and coastal sites near waste water discharges -sediment areas near sites given above -the main research interest will be focused on the following compounds: Carbamazepine, Diclofenac, naproxen, octatetracycline, ciprofloxacin, sulfadiazine and Metformin

Country	Switzerland
Targeted compounds	beta-blockers, 37%, 44% and 50% for Sotalol, Propranolol, Metoprolol and Atenolol, respectively. These results are also confirmed by measurements in two municipal STPs for Atenolol, Sotalol and Propranolol. The estimated eliminations are slightly too high for Metoprolol.
Period	2007
Matrices	Effluents
Responsible Agency	
Contact	Alfredo.Alder@eawag.ch
Reference/abstract	Elimination of b-blockers in sewage treatment plants. M. Maurer_, B.I. Escher, P. Richle, C. Schaffner, A.C. Alder. b-Blockers are used to treat high blood pressure as well as patients recovering from heart attacks. In several studies, they were detected in surface water, thus indicating incomplete degradability of these substances in sewage treatment plants (STPs). In this study, we determined the sorption coefficients (KD) and degradation rates of the four b-blockers Sotalol, Atenolol, Metoprolol and Propranolol in sludge from an STP operating with municipal wastewater. The sorption coefficients (KD, standard deviations in brackets) were determined as 0.04(70.035), 0.04(70.033), 0.00(70.023) and 0.32(70.058) L g_1 COD, and the pseudo-first-order degradation rate constants were estimated to be 0.29(70.02), 0.69(70.05), 0.58(70.05) and 0.39(70.07) L d_1 g_1 COD for Sotalol, Atenolol, Metoprolol and Propranolol, respectively. These values translate into a typical elimination in STPs (sludge concentrations of 4gCOD L_1 and a hydraulic retention time of 6 h) of 25%,

Country Romania

Targeted compounds This work was financed by the The reported study was performed in the project PHARMSOMES focusing on environmental exposure of pharmaceuticals in the Somes Valley Watershed in Romania. Compounds studied: several pharmaceuticals (see publication) Matrices studied: wastewater and surface water

Period No

Matrices

Responsible Agency Swiss National Science Foundation (SNSF), the Swiss Agency for Development and Cooperation (SDC) and the Romanian Ministry for Education and Research (MEC) within the framework of the Swiss-Romanian cooperation programme on "Environmental Science and Technology in Romania - ESTROM".

Contact Alfredo.Alder@eawag.ch

Reference/abstract An overview of pharmaceuticals and personal care products contamination along the river Somes watershed, Romania Zaharie Moldovan, Gabriella Schmutzer, Florina Tusa, Roxana Calin and Alfredo C. Alder The mass flows of selected pharmaceuticals and personal care products (PPCPs) were studied in the aqueous compartment of the river Somes in Romania. PPCPs were measured in wastewater treatment effluents and in the receiving river water. The analytical method for the determination of PPCPs in river water was based on solid phase extraction and GC-ITMS. Carbamazepine, Pentoxifylline, ibuprofen, diazepam, Galaxolide, Tonalide and Triclosan were determined in wastewater effluents with individual concentrations ranging from 15 to 774 ng L_1. Caffeine was measured at concentrations up to 42 560 ng L_1. Due to the high contamination of WWTP effluents, the receiving river was also polluted. The most abundant PPCPs measured in the Somes were caffeine, Galaxolide, Carbamazepine and Triclosan. They were present at all the 15 sampling sites along the Somes, the concentrations ranging from 10 to 400 ng L_1. The concentrations in the effluents of the different wastewater treatment plants (WWTPs) varied considerably and the differences are due to different elimination efficiencies of the studied PPCPs during sewage treatment. Only one of 5 WWTPs studied, the WWTP in Cluj-Napoca, was working properly, and therefore technical measures have to be taken for upgrading the WWTPs and reducing the environmental load of micro pollutants. This study is the first overview of PPCPs along on Romanian part of river Somes.

10.3. Abbreviations

30S	Small ribosomal sub-unit (bacteria)
ACR	Acute/chronic ratio
AHDI	Phantolide
AHTN	Tonalide
ASE	Accelerated solvent extraction
ATC	Anatomical therapeutical chemical
ATII	Traseolide
ATP	Adenosine tri phosphate
BCF	Bioconcentration factor
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
CAN	Centralförbundet för alkohol- och narkotikaupplysning
CAS	Chemical abstract service
CADG	Cocamidopropyl betaine
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nerve system
COX	Cyclooxygenase
CYP	Cytochrome P450
DBP	Dibutyl phthalate
DDD	Defined daily dose
DEET	Diethyltoluamide
DEHA	Di ethylhexyl adipate
DEHP	Diethylhexyl phthalate
DNA	Deoxyribose nucleic acid
ECOSAR	Ecological Structure Activity Relationships
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMEA	European Pharmaceuticals Evaluation Agency
ERA	Environmental risk assessment
EPA	Environment protection agency
ESI	Electrospray ionisation
EQS	Environmental quality standard
FDA	Food and drug administration
GABA	Gamma amino butyric acid
GS/MS	Gas chromatography mass spectrometry
HCOOH	Formic acid
HHBC	Galaxolide
HMG-CoA	3-hydroxy-3-methyl-glutaryl-Coenzyme A
HP	Humans pharmaceuticals
Ibu–OH	Hydroxylated metabolite of Ibuprofen
Ibu-COOH	Acid metabolite of Ibuprofen
IVL	Institut för vatten och luftforskning
LC-MS	Liquid chromatography mass spectrometry
LLE	Liquid-liquid extraction
LPME	Liquid phase micro extraction
MDM	Octamethyltrisiloxane
MDMA	Methylenedioxymethamphetamine (ecstasy)
MD2M	Decamethyltetrasiloxane
MD3M	Dodecamethylpentasiloxane
MEC	Measured environmental concentration
mLOD	Method limit of detection
mLOQ	Method limit of quantification
MM	Hexamethyldisiloxane
MW	Molecular weight

NIH	National institute of health
NIVA	Norsk institutt for vannforskning
NOK	Norwegian kroner
NSAIA	Non steroidal Anti-Inflammatory Agents
NSAID	Non steroidal Anti-Inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
PCP	Personal care products
PDMS	Poly-dimethylsiloxane
PEC	Predicted environmental concentration
pKa	Dissociation constant
PNEC	Predicted no effect concentration
PPCP	Pharmaceutical and personal care products
QSAR	Quantitative Structure Activity Relationships
RNA	Ribose nucleic acid
SEPA	Scottish environmental protection agency
SPE	Solid phase extraction
SRC	Syracuse Research Corporation
SSRI	Selective serotonin reuptake inhibitors
STP	Sewage treatment plant
TCA	Tri cyclic antidepressants
THC	Tetra hydro cannabinol
UNODC	United Nations Office on Drugs and Crime
USDEA	United States Drug Enforcement Agency
USFDA	United States Food and Drug Administration
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products
VLDL	Very low density lipoproteins
WHO	World health organisation
WTP	Wastewater treatment plants
WTW	Wastewater treatment works
ZPT	Zinc pyrithione

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Tittel - norsk og engelsk
Human- og veterinærlegemidler, narkotika og kosmetiske produkter i miljøet
Kunnskapsstatus og overvåkingsbehov

Human and Veterinary Pharmaceuticals, Narcotics, and Personal Care Products in the Environment
Current State of Knowledge and Monitoring Requirements

Sammendrag – summary
Mange tonn human- og veterinærlegemidler blir solgt i Norge hvert år. Store mengder narkotika blir konsumert illegalt. Det omsettes kosmetiske produkter for flere milliarder kroner hvert år. Disse produktgruppene blir ofte omtalt under fellesbetegnelsen PPCP som står for **P**harmaceuticals and **P**ersonal **C**are **P**roducts. I denne rapporten gis en oversikt over dagens kunnskap om miljøeffekter av PPCP i Norden, anbefalinger om hvilke stoffer som bør miljøovervåkes ytterligere, hvilke nye stoffer som bør inkluderes, samt lokaliteter og matrikser som skal inngå i fremtidige overvåkings-prosjekter i Norge og Norden.
Many tonnes of human and veterinary pharmaceuticals are sold in Norway every year, whilst it is estimated that many kilos of narcotics are illegally used. The personal care products market in Norway is worth several billion NOK a year. These xenobiotic compounds (human and veterinary pharmaceuticals, narcotics, and personal care products) are often combined under the common heading: Pharmaceuticals and Personal Care Products (PPCPs). This report give an overview of the current state of knowledge regarding the occurrence of these compounds in the Nordic environment, provide an overview of the environmental effects of PPCPs, and recommend which compounds that should be included in future monitoring programs.

4 emneord Legemidler, narkotika, kosmetiske produkter, miljø	4 subject words Human and Veterinary Pharmaceuticals, Narcotics, and Personal Care Products in the Environment

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SFT skal bidra til å skape en bærekraftig utvikling. Vi arbeider for at forurensning, skadelige produkter og avfall ikke skal føre til helseskade, gå ut over trivselen eller skade naturens evne til produksjon og selvfornyelse.

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