





# Retrospective environmental risk assessment of human pharmaceuticals in the Nordic countries 1997-2007

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**Retrospective environmental risk assessment of human pharmaceuticals in the Nordic countries 1997-2007**

TemaNord 2009:587

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ISBN 978-92-893-1954-6

Copies: 0

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# Preface

## Retrospective environmental risk assessment of human pharmaceuticals in the Nordic countries 1997–2007

In 2008 IVL Swedish Environmental Research Institute and the project group “Cosmetics and pharmaceuticals in the environment”, within Nordic Chemicals group (NKG), received funding from the Nordic Council of Ministers – while Norway was holding the presidency – for a special publication concerning the consumption of human pharmaceuticals and the assessment of the corresponding environmental risk, during the period 1997–2007.

Norway, represented by Kari Løkken, has had the main responsibility for the project in cooperation with the consultant Andreas Woldegiorgis (IVL). The project reference group has had the following members:

Kari Løkken, Norwegian Pollution Control Authority (SFT), Norway, Lars Haug Andersen, Norwegian Pollution Control Authority (SFT), Norway, Anna-Karin Johansson, Medical Products Agency (LV), Sweden, Flemming Ingerslev, Danish Environmental Protection Agency, Denmark, Laila Sortvik Nilssen, Norwegian Medicines Agency, Norway, Eirik Grønevik, Norwegian Medicines Agency, Norway, Virpi Virtanen, Finnish Environment Institute, Finland, Elin G. Gudmundsdottir, Environment Agency of Iceland.

2008 beviljades en gemensam ansökan ifrån IVL Svenska Miljöinstitutet och projektgruppen ”Miljöfarliga ämnen i läkemedel och kosmetika” (inom Nordiska Kemikaliegruppen, NKG) av Nordiska Ministerrådet, för en specialpublikation om läkemedelskonsumtion och en bedömning av de associerade miljöriskerna, avseende perioden 1997–2007.

Norge, representerat av Kari Løkken, har haft huvudansvaret för projektet, i samarbete med den utförande konsulten Andreas Woldegiorgis (IVL). Projektets referensgrupp har haft följande sammansättning:

Kari Løkken, Statens forurensningstilsyn (SFT), Norge, Lars Haug Andersen, Statens forurensningstilsyn (SFT), Norge,

Anna-Karin Johansson, Läkemedelsverket (LV), Sverige

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# Summary

## The increased consumption of human pharmaceuticals in the Nordic countries

New pharmaceutical substances are constantly being introduced and marketed in the world and the consumption of human pharmaceuticals has been rapidly increasing in the Nordic countries over the last decades (OECD, 2008). Investigations on the matter indicate that the consumption of human pharmaceuticals have increased more rapidly in the Nordic countries, particularly in Sweden, than in the “average” European country (OECD, 2007).

Pharmaceuticals are by necessity often rather persistent and hence, not readily biodegradable. Depending on the classification criteria used they are mostly rated as potentially persistent or at least have proven to have rather low biodegradation rates in the environment (Daughton and Terne, 1999, Lam et al., 2004, Aga, 2007, Gibs et al., 2007). The intrinsic persistence of pharmaceuticals often stems from the fact that an active substance may need to pass the gastrointestinal tract prior to absorption and distribution in the correct bodily compartment (where the therapeutic effect is expected to occur). Also, very rapidly metabolised pharmaceuticals would make it very difficult to maintain the therapeutic concentration of the drug in the blood plasma; such pharmaceuticals are mostly being administered through constant infusion.

Furthermore, pharmaceuticals are intentionally designed to have a biological effect (as a receptor agonist or antagonist), and the effects mostly occur at rather low plasma concentrations in humans (~ mg/l). There are of course examples of pharmaceuticals without any receptor specificity such as electrolytes but the overwhelming majority of pharmaceuticals target certain receptors. The conservation of the biological receptors throughout the evolution of species renders it very likely that a potent human pharmaceutical will also affect other species at rather low effect concentrations even though the receptor response might be different from the response induced in humans (Borenstein et al., 2007, Coronado et al., 2007, Gunnarsson et al., 2008).

Finally, since the consumption pattern of human pharmaceuticals is mostly seasonally independent, and the substances are often persistent, the organisms being exposed to pharmaceutical residues may very well live their entire life constantly exposed to a low concentration of drugs.

## The environmentally hazardous properties identified in pharmaceutical substances

Pharmaceutical residues (stemming from both human and veterinary drugs) have been recognized as a potentially hazardous group of substances with respect to the aquatic environment (Halling-Sørensen et al., 1998, Zuccato et al., 2001, Zwiener et al., 2001, Jones et al., 2002, Ferrari et al., 2003 & 2004, Costanzo et al., 2005). Several high volume sales drugs such as NSAIDs,  $\beta$ -blockers and contraceptives have shown to induce detrimental effects in different test species (algae, crustaceans and fish) at low effect concentrations when tested in the lab. Other types of pharmaceuticals such as clofibric acid and carbamazepine have been found to act by a non-specific mode of action (non-polar narcosis), and with *Daphnia* as tested species the combination effect of these substances followed the concept of concentration addition, while in the case of algae as test species the concept of independent action could be used to calculate the mixture toxicity. The anti-inflammatory drugs diclofenac and ibuprofen have also been found to act unspecific by non-polar narcosis and to follow the concept of concentration addition in the algae test as well as in the *Daphnia* test (Michael Cleuvers, 2003). From studies internationally (Europe, North America and Japan) the general observations is that the chronic lowest observed effect concentrations (LOEC) in standard laboratory organisms are about two orders of magnitude higher than maximal concentrations in STP effluents, for most of the pharmaceuticals being investigated so far (Fent et al., 2006). For diclofenac, the LOEC for fish toxicity was in the range of wastewater concentrations, whereas the LOEC of propranolol and fluoxetine, with regard to zooplankton and benthic organisms, were near to maximal measured STP effluent concentrations (Fent et al., 2006). In surface water, pharmaceutical residue concentrations are lower and thus also the calculated environmental risks. However, targeted ecotoxicological studies are lacking almost entirely and such investigations are needed focusing on subtle environmental effects. Despite the lack of data, some pharmaceuticals (especially contraceptives) have also been strongly suspected to induce effects in field studies as well (Brian et al., 2007, Kidd et al., 2007, Vajda et al., 2008).

The increased overall consumption and the increasing number of active substances being sold (the growing number of potential drug targets being exploited) will of course pose an ever increasing environmental risk.

In many of the Nordic countries screening studies of pharmaceutical residues in effluent water streams from waste water treatment plants (WWTPs), in sludge, in sediment and in biota, showed detectable levels of a vast range of different pharmaceuticals (Andersson et al., 2006, Woldegiorgis et al., 2007, Ashton et al., 2004, Roberts et al., 2006 and Thomas K.V, 2007). Evaluation of the possible environmental consequences of these findings is very difficult to assess however, since there

is a vast variation in the reported concentrations of pharmaceuticals. Screening efforts are mostly based on a limited number of samples.

Another complicating matter is the fact that more than 1000 different active substances are currently being sold in the Nordic countries while screening studies can only cover a handful of the total variety of drugs.

Consequently, it is of utmost importance to implement another tool to assess environmental risks.

## Environmental risk assessment of pharmaceuticals

In the Nordic countries reliable, spatially resolved sales data of human pharmaceuticals are available, sometimes going back several decades. This is rather unique in a global perspective and can be exploited for the purpose of environmental risk assessment. In this study, sales data from the Nordic countries going back a decade in time (the period 1997–2007) have been compiled, sorted and converted into PEC-values (PEC = Predicted Environmental Concentrations in the surface water).

Based on the compilation of PEC data, additional information on the top 30–40 drugs (with respect to defined daily doses as well as number of kg sold) was compiled. For instance data on toxicity, biodegradation rates and bioaccumulation potential was compiled.

For the top-selling pharmaceuticals a retrospective environmental risk assessment was made, based on the sales over the preceding decade (based on PEC/PNEC-quotients). In an attempt to also account for differences in biodegradation rate between different top-selling drugs, a 'time resolved' PEC/PNEC equation has been introduced. In the time resolved risk assessment data on biodegradation from the Swedish risk and hazard classification scheme on [www.fass.se](http://www.fass.se) (see 2.7) have been utilised (four degrees of biodegradation rate). In short, if the substance was classified in [fass.se](http://www.fass.se) as '*Ready biodegradable*' a small fraction, 10 % of the sold amount, is assumed to be present in the environment after 12 months (a linear degradation rate independent of concentration, 17.5%, degradation/month). On the other extreme, if the [fass.se](http://www.fass.se) website classified the pharmaceutical as "*Persistent*" the large fraction of the sold amount still remaining in the environment after 12 months is assumed to be 80 % (this corresponds to a degradation rate of 1.8 % degradation/month. Between "*Ready biodegradable*" and "*persistent*" also the classes "*Inherently biodegradable*" and "*Slowly degradable*" (corresponding to linear degradation rates of 12,6 and 7,35 % per month, respectively or 20% and 40 % being left in the environment after 12 months). Assuming a 0<sup>th</sup> order kinetics for biodegradation is of course questionable (it is probably a correct assumption when the environmental concentration of a substance is significantly heightened). However, by imposing data on the persistence it will be possible to account for concentration build-up in the PEC/PNEC-ratio for some of the drugs. When-

ever the *fass.se* database suggests that a substance is accompanied with high removal rates in typical Nordic WWTPs, or seem to be highly metabolised prior to excretion, the PEC-value of that substance is also slightly adjusted (decreased), or commented on in the text.

Since the time frame of the retrospective environmental risk assessment is only 10 years (a relatively short time frame), the comparison between the EMEA-based, instantaneous PEC/PNEC-quotients, and the “time-resolved” PEC/PNEC-quotients also taking biodegradation rates into account, is illustrative of the very different regimes of environmental risk different substances will occupy.

A striking observation is also the fact that the consumption of pharmaceuticals is very similar in the Nordic countries. National differences between countries seem subtle and may in some cases stem from the fact that the sales statistics are of varying quality.

In all Nordic countries pharmaceuticals containing the estrogenic hormones (estradiol, ethinyl estradiol and estriol) are the ones which, by far, have the highest environmental risk. National PEC/PNEC-quotients well over 10–20, as in the case of estradiol, indicate both an alarmingly high risk (aquatic organisms in receiving waters have probably already suffered from the exposure), along with further questions as how to calculate the total consumption and emission when several formulations on the market lacks defined daily doses (DDDs).

Also taking the biodegradation rates into consideration renders the estrogens the top position in terms of the accumulated environmental risk.

# 1. Ever increasing consumption of human pharmaceuticals?

## 1.1 Increased consumption of pharmaceuticals

The constant increase in medicines consumption, observed through the nineties, still continues in all Nordic countries (Figure 1). This can largely be attributed to the growing fraction of elderly people in the population, having a higher propensity of getting several diseases and afflictions. In all countries in Western Europe the share of elderly people in the population is increasing. According to new demographic studies, the total population in Western Europe gained its peak level in terms of number of inhabitants in 2005 and are now expected to decline, immigration not fully considered (UN, 1998). This is mainly due to the current fertility numbers within the EU attributed to a reproductive level below 2.1 children per fertile woman. In parallel with the decreased fertility, the average life expectancy within the EU has increased. The quotient between adults of working age (15–64 years) and the part of the population being older than 64 years has changed dramatically (the PSR, the Potential Support Ratio). In Sweden PSR has changed even more than the rest of the Nordic countries, and are expected to continue in that manner. According to Swedish statistics the number of people older than 65 years, which is high in Sweden today (> 17 % of the total population), will increase with 845 000 until the 2050, an increase of approximately 55 %, and then encompass 23–27 % of the total population (UN, 2000, SCB 2001a). Within this group, the group of people being older than 80 years will have increased by 100 % by 2050.

Old people often have a high demand for medicines, since numerous diseases are related to age (Thorslund et al., 2004). An increasing number of people are thus in need of medicines (Socialstyrelsen., 1999 & 2003). From the demographic prognosis, it seems as if the overall consumption of pharmaceuticals is inclined to increase throughout the first half of this century generally within the EU and particularly in the Nordic countries.

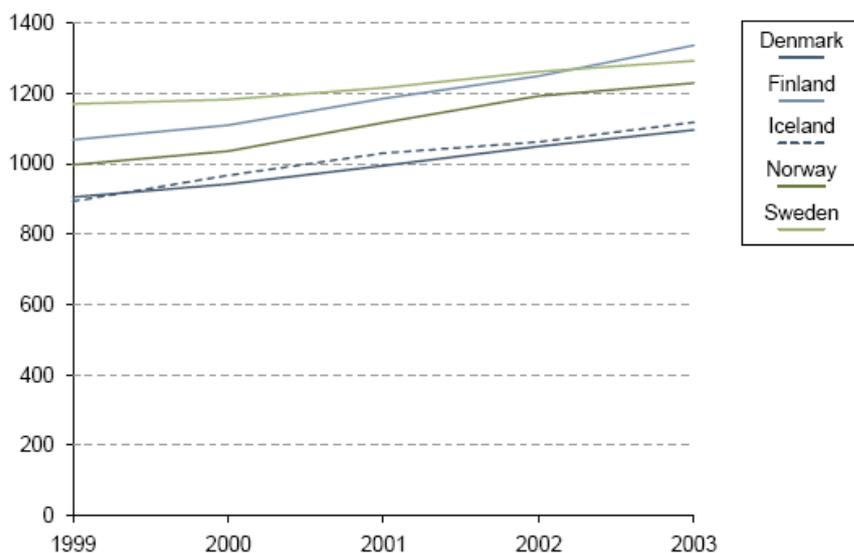


Figure 1. Sales of medicinal products in the Nordic countries 1999–2003, in nr of DDDs/1000 inhabitants/day (figure taken from NOMECSO, 2004).

Also, during the last decade of the 20th century quite many new medicines were launched and marketed, not only as more or less improved modifications of existing drugs, but also for the treatment of ailments previously considered untreatable. Furthermore, today it is increasingly common to use a combination of several drugs instead of a single substance in the treatment of many diseases, *e.g.*, hypertension, rheumatoid arthritis and gastric ulcer. Along with the increasing consumption come increased costs for the health care systems in the Nordic countries. There have been some reports on early apprehensions of the possible environmental effects as well (for instance the risk of development of antibiotic resistance in bacteria from STP sludges, Lindberg R, thesis).

## 1.2 Novel drugs

A rapid flow of new medicines was seen during the last decade before the turn of the millennium. These drugs included *e.g.* antihypertensives (angiotensin II antagonists), new substances for the treatment of epilepsy, triptanes used against migraine, inhaled long-acting beta-2-agonist against asthma and chronic obstructive pulmonary disease (COPD), several antipsychotic drugs, and prostaglandin analogues against glaucoma. Other examples of new therapies developed primarily during the late 1990s are treatment of Alzheimer's disease, which started in the nineties and the drugs for its treatment are consumed increasingly. Pioglitazone and rosiglitazone are insulin sensitizers, oral antidiabetic medicines with a new mechanism of action. Another group of new drugs are the oral anti-diabetics, repaglinide and nateglinide, which increase insulin secretion.

Treatment of erectile dysfunction has become more common after introduction of oral treatment with sildenafil and its analogues.

However during the recent years very few new substances have been launched and entered the market, compared to the situation in the 1990's. Often, new launches have been with analogues of old drugs rather than completely new substances; such as triptanes for the treatment of migraine, proton pump inhibitors to inhibit gastric acid secretion, and angiotensin II antagonists for hypertension. Also, stereoisomers of many old drugs were introduced, e.g. desloratadine, esomeprazol, escitalopram and levocetirizin.

According to the international pharmaceutical industry and its representatives, this "clogging of the launching pipe line" is a major cause for concern within the industry (pers. commun.).

Also, during the past few years some important medicines – e.g. citalopram, simvastatin, omeprazol and felodipin – have lost their patent protection. This, along with the generic substitution, has led to decreased prices and a relatively small increase in medicine expenditure in all Nordic countries.

### 1.3 Market authorisation

In all the Nordic countries a marketing authorisation can be granted in three ways defined in EU legislation: through the centralized procedure, through the decentralised procedure (used for applying for a market authorisation in cases where the product is not yet authorised in any EU member state)<sup>1</sup> through the mutual recognition procedure, or through the national procedure. For all new medicines a marketing authorisation may be applied for through the centralized procedure. Certain new medicines, i.e. biotechnologicals and other innovative medicines, use this procedure. A marketing authorisation granted through the centralized procedure allows for marketing in all EU and EEA countries. The professional handling of the applications is performed by the EMEA, the European Medicines Agency, which must reach a decision within 210 days after filing of the application (not including the days the applicant uses to answer further questions from the authorities). The scientific evaluation of the application is performed by a team of experts affiliated with national authorities in the EU member states and not from EMEA itself. When the marketing authorisation is granted centrally, all its variations (new indications, administration forms, strengths, etc.) are also handled centrally. A national marketing authorisation valid in one EU country may form the basis for an application for a marketing authorisation by the mutual rec-

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<sup>1</sup> In contrast, at the start of the mutual recognition procedure (MRP), the product is authorised in one or several member states. The applicant asks one member state to act as a Reference Member State (RMS). The RMS prepares a preliminary SPC, package insert, labelling and an assessment report for the product. The maximum duration of this phase is 120 days.

ognition procedure in other EU countries (as well as the EFTA countries), which have 90 days to reach their conclusion. An application via the mutual recognition procedure is from 1st January 1998 compulsory for all medicines for which a marketing authorisation in more than one EU country is applied for, and where the centralized procedure is not used. If marketing authorisation is applied by the national procedure, it shall be processed in a maximum of 210 days. The national procedure is still employed for applications concerning variations of old nationally approved medicines, and marketing authorisations of parallel imports.

# 2 Environmental risk assessments of human pharmaceuticals

## 2.1 Background

Environmental risk assessment (ERA) of human pharmaceuticals has been conceptually developed by the National authorities like Federal Drug Administration agency in the US (FDA) and later on, also by The European Medicines Agency (EMA).

It is important to stress the difference between risk and hazard since these two concepts are often used synonymously while they basically describe different things.

The environmental hazard associated with a human pharmaceutical is referring to the intrinsic properties of the substance such as the toxicity of the substance, the persistence of the substance or the potential to bioaccumulate. The environmental risk, on the other hand, weighs the hazard potential against an estimate of the exposure level (the consumption or the sales). Thus, a very toxic and persistent substance that is only sold in minute quantities (kilograms or grams) does not pose any environmental risk, while a relatively harmless (substance of low toxicity) substance with annual sales of 80–90 tonnes may be associated with an environmental risk regardless of the non-hazardous intrinsic properties. The risk and hazard assessment is thus partly complementary.

## 2.2 Exempted substances

Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are normally exempted because they are “unlikely to result in significant risk to the environment”. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents“ (CPMP/SWP/4447/00, 2006).

Since the technical guidance document does not apply to medicinal products consisting of genetically modified organisms (GMOs), nor radio pharmaceutical precursors for radio-labelling and radio-pharmaceuticals, these groups have also been purposely omitted.

## 2.3 Sales data

The figures used in this description of the medicines consumption in the Nordic countries are based on sales data. Where in the sales chain the data are collected varies between the countries. Norway, Iceland and Finland have all supplied data from wholesalers to pharmacies and hospitals, whereas Denmark, Sweden and Iceland (only for 2007) supplied data from both pharmacy sales to individual consumers and hospital sales to individual wards. Depending on where in the sales chain data are collected, various levels of accuracy can be reflected in the resulting statistical representation.

## 2.4 Prescription vs. Over-the-counter sales

There is also a difference between the countries with respect to which medicines are sold on prescription only and which are sold over-the-counter. In Denmark, Iceland and Norway over-the-counter medicines may also be sold on prescription, so that special patient groups, such as the elderly population or chronically ill patients, may get their expenses reimbursed. Whether a medicament is sold on prescription or over-the-counter may influence the consumption. In Sweden and in Norway OTC drugs may be sold on prescription and be included in the reimbursement system if the drug is needed for continuous treatment during at least one year or for repeated treatment for at least three months per treatment period. In Finland some OTC drugs – mainly basic creams or antifungal or cortisone preparations for skin diseases, eye drops and vitamins in severe diseases – can be reimbursed when prescribed by a physician

## 2.5 Use of the ATC and DDD classification

All medicines are classified according to the ATC classification (Anatomical Therapeutic Chemical Classification System). The ATC system divides the medicinal substances for human use into 14 anatomical main groups (1st level), with 2 therapeutic/pharmacological subgroups (2nd and 3rd levels), a chemical/therapeutic/pharmacological subgroup (4th level), and finally a subgroup for the chemical substance (5th level). A complete classification of the blood glucose lowering agent metformin, with the ATC code A10BA02, illustrates the structure of the ATC system:

- A Alimentary tract and metabolism (1st level, anatomical main group)
- 10 Drugs used in diabetes (2nd level, therapeutic main group)
- B Oral blood glucose lowering drugs (3rd level, therapeutic/pharmacological subgroup)

- A Biguanides (4th level, chemical/ therapeutic/pharmacological subgroup)
- 02 Metformin (5th level, subgroup for chemical substance)

Medicines sales in amount of active substances are in this presentation expressed using Defined Daily Doses (DDDs), as defined and assigned by the WHO. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The use of DDDs as a unit of measurement allows for comparisons of drug consumption irrespective of differences in price and strength between various formulations.

For some medicine groups, such as cytostatics, dermatologicals, and ex tempore preparations, the assignment of DDDs is not possible. Furthermore, there is no WHO-DDD available for most gels, dermal patches and vagitories. In those specific cases, this project have calculated “in-house variants“ of daily doses, based on the UD (= active ingredient per unit dose), as specified in the prescriber’s guidance to Swedish doctors ([www.fass.se](http://www.fass.se)). These figures have then been used also for the analysis of sales from Denmark, Finland, Norway and Iceland. There will of course be a source of error, however most products (product formulations) are similar in the Nordic countries.

Sales presented in amount of active substance are usually expressed in DDDs/1000 inhabitants/day. This improves the possibility of comparing therapeutic groups internationally and regionally and studying consumption trends over time. This unit is calculated as follows:

$$\frac{Tot\_Consumpt\_in\_DDDs \cdot 1000}{365 \cdot number\_of\_inhab.} \quad \text{Eq. 1}$$

This figure gives an estimation of what proportion of the population receives a certain drug treatment. An amount of 50 DDDs per 1 000 inhabitants means that 50 people out of 1 000, i.e. 5% of the population, use the substance in question on a daily basis. This share is however only an estimate, which presupposes that all sold medicines are consumed (or flushed down the drain), that the prescribed daily dose agrees with the DDD, and that the medicine is taken every day of the year. In reality these criteria are seldom met.

## 2.6 Scientific basis of the Environmental Risk Assessment (ERA)

The environmental risk assessment (the ERA) is based on the calculation of a predicted environmental concentration (the PEC-value) which is

basically an assessment of the magnitude of the exposure. The PEC-value is then compared with the toxicity of the substance in the form of an estimate of the 'highest tolerable concentration of the substance in the aquatic environment without any harm for the organisms living there'; the Predicted No Effect Concentration (the PNEC-value). Based on the assumption that all consumption of pharmaceuticals is excreted into affiliated sewer systems, passing a WWTP, the PEC-calculation is restricted to the aquatic compartment and consequently, the PNEC-value refers to toxicity towards aquatic species.

The initial calculation of PEC in surface water assumes:

- The predicted amount used per year is evenly distributed over the year and throughout the geographic area.
- The sewage system is the main route of entry of the drug substance into the surface water.
- There is no biodegradation or retention of the drug substance in the sewage treatment plant (STP).
- Metabolism in the patient is not taken into account.

The following formula can be used to estimate the PEC in the surface water (Sebastine and Wakeman, 2003):

$$PEC_{surface\_water} [\mu g / l] = \frac{A \cdot 10^9 \cdot (100 - R)}{365 \cdot P \cdot V \cdot D \cdot 100} \quad \text{Eq. 2}$$

A (kg/year) = total actual API sales (active moiety) nationally, for a certain year. The A-value can be retrieved from the number of DDDs sold multiplied with the WHO-DDD definition. R (%) = removal rate in the WWTP (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available. P = number of inhabitants in the country. V (l/day) = volume of wastewater per capita and day = 200 (default value used). D = factor for dilution of waste water by surface water flow = 10 (default value used).

In the technical guidance document developed by the European Medicines Agency (EMA), the PEC-values are based on the following calculation;

$$PEC_{surf.water} = \frac{DOES_{ai} \cdot F_{PEN}}{WASTEWinhab \cdot DILUTION} \quad \text{Eq. 3}$$

In which the *DOES<sub>ai</sub>* represents the maximum daily dose consumed per inhabitant,

$F_{PEN}$  denotes the market penetration factor of the particular brand (0.01 default).

$WASTEWinhab$  is the amount of wastewater per inhabitant and day (200 litres by default), and  $DILUTION$  represents the dilution factor going from STP effluent concentration to recipient water concentration (10, by default). The main advantage of Eq. 3 is that it can be used to calculate PEC-values also for pharmaceuticals in the process of entering a market (when no sales data are available). However, for the purpose of this report; the retrospective assessment of the environmental risks, eq. 2 renders by much more realistic assessments of the predicted environmental concentrations (Grung et al., 2008).

As for the assessment of substance toxicity, a standard long-term toxicity test set on fish, daphnia and algae normally used to determine the predicted no-effect concentration ( $PNEC_{WATER}$ ). Such tests should preferentially be performed according to standard protocols (see below) for maximum comparability.

<i>Algae</i>	Growth Inhibition Test OECD 201
<i>Daphnia</i>	Reproduction Test OECD 211
<i>Fish</i>	Early Life Stage Toxicity Test OEC 210

Also a respiratory test on active sludge is conducted (OECD 209). The OECD 209 test assesses the effect of a test substance on micro-organisms by measuring the respiration rate under defined conditions in the presence of different concentrations of the test substance. The purpose of the OECD 209 test is to provide a rapid screening method whereby substances which may adversely affect aerobic microbial treatment plants can be identified, and to indicate suitable non-inhibitory concentrations of test substances to be used in biodegradability tests.

Short-term testing is generally not recommended for human pharmaceuticals which are fairly rational since continuous exposure of the aquatic environment via STP effluents can be assumed. However, for the vast majority of pharmaceutical substances there are only data on the acute ('short-term') toxicity available. The predicted no effect concentration (PNEC) is calculated by applying an assessment factor (AF) to the no-observed-effect-concentration(s) (NOEC) from relevant effect studies. The AF is an expression of the degree of uncertainty in the extrapolation from the test data on a limited number of species to the actual environment.

An assessment factor of 1000 is normally applied to the most sensitive of three short-term toxicity (LC/EC<sub>50</sub>) endpoints as described in the EU technical guidance document (TGD) [European Commission 2003]. However, the assessment factor may be reduced to 100, 50 or 10, depending on the number of long-term NOEC endpoints available, providing long-term data are available for the species with the lowest acute LC/EC<sub>50</sub> (see Table 1).

The use of assessment factors for the assessment of acute toxicity data is not an approved operation by EMEA guideline (EMEA, 2006) since only long-term toxicity data should be used;

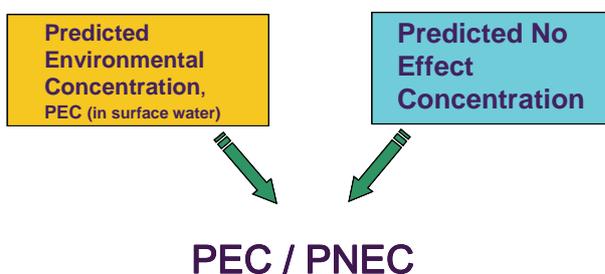
“The predicted no effect concentration (PNEC) is calculated by applying an assessment factor (AF) to the no-observed-effect-concentration(s) (NOEC) from relevant effect studies. The AF is an expression of the degree of uncertainty in the extrapolation from the test data on a limited number of species to the actual environment.

The PNEC<sub>WATER</sub> is based on the lowest NOEC result from the base set long-term toxicity tests. “

**Table 1. Assessment factors used depending on the number of toxicological endpoints available.**

Available data	Safety Factor
At minimum <b>one</b> acute assay at one trophic level (Algae, Daphnia or Fish)	1,000
<b>One</b> longterm, chronic toxicity assay (NOEC): with Fish or Daphnia	100
<b>Two</b> longterm, chronic toxicity assays (NOEC) at <b>two</b> trophic levels: Algae and/or Daphnia and/or Fish	50
<b>Three</b> longterm, chronic toxicity assay at <b>three</b> species (NOEC): Algae, Daphnia and Fish ( <b>three</b> trophical levels)	10

If the PEC/PNEC quotient is well below unity ( $PEC/PNEC \ll 1$ ), the environmental risk associated with the substance is regarded as low, acceptable or even insignificant. Conversely, if the PEC/PNEC quotient is well over unity ( $PEC/PNEC \gg 1$ ), environmental risk associated with the substance is regarded as moderate, unacceptable or even high (see Figure 2).



*Figure 2. The basis of the PEC/PNEC-quotient in environmental risk assessment.*

## 2.7 Hazard classification

Beside the toxicity there are other characteristics of a pharmaceutical that can be very detrimental to the environment. The persistence of a chemical, basically the propensity to withstand fast biodegradation ultimately enhances the toxicity of the pharmaceutical. Since persistence can yield accumulation of the substance in the aquatic environment (constant tributary can be assumed regarding pharmaceuticals), a drug that possesses rather low toxicity can eventually reach effect concentration levels.

Persistence or biodegradation kinetics is measured in standardized tests, often using activated sludge inoculums (OECD 301–302), or in sediments with a varying degree of organic carbon (OECD 308). Normally a pharmaceutical company in the registration process is requested to provide data on both the OECD 301 as well as 308 tests unless the substance passes the criteria of the OECD 301 test (and hence being classified as *ready biodegradable*).

On the initiative of The Swedish Association of the Pharmaceutical Industry, LIF, Sweden has, as the first country in the world, introduced a voluntary system for environmental classification of pharmaceuticals. The classification system, herein referred to as the “fass.se database” is a web portal where environmental risk- and hazard information on human pharmaceuticals have been published by the pharmaceutical companies producing them.

In the fass.se website human pharmaceuticals have been classified regarding their persistence. Depending on which tests the pharmaceutical has passed or not, three possible classes are used;

“The medicine is degraded in the environment (passed an OECD 301 test).

“The medicine is slowly degraded in the environment” (passed an OECD 302 test).

Or

“The medicine is potentially persistent“ (failed the OECD 301/302 tests, no data on abiotic degradation rate that substantiate any of the aforementioned classes)

Along with persistence also the propensity of a pharmaceutical to bioaccumulate can ‘amplify’ the environmental impact of toxicity of the substance. The bioaccumulation is a measure of the degree of enrichment in bodily tissue. Again, a moderately toxic pharmaceutical present in the environment in minute concentrations (corresponding to a low PEC-value) can reach concentrations in fish tissue that are 1 000 – 1 00 000 times higher if the pharmaceutical is bioaccumulative (occurs within a trophic level, and is the increase in concentration of a substance in an individuals' tissues due to uptake from food and sediments in an aquatic

milieu) and/or if the substance and has a corresponding bioconcentration factor, BCF) (Suedel et al., 1994, and Landrum and Fischer, 1999).

In the fass.se context a pharmaceutical is considered as bioaccumulative if the partition coefficient of the substance between n-octanol and water, the Kow, exceeds 1000 (or the log Kow >3). According to EMEA, the partition coefficient, Kow, should numerically exceed 36 623 (or log Kow > 4.5) to yield the classification of bioaccumulative.

Unfortunately, neither persistence nor bioaccumulation is taken into consideration in 'normal' state-of the art ERAs.

## 2.8 Alternative risk assessment also taking persistence into consideration

To attempt to account for persistence in the risk assessment (the PEC/PNEC evaluation) the following approach is suggested and used.

The data on persistence from the fass.se database have been re-interpreted to yield four classes (4), based on the persistence testing fail/pass of each pharmaceutical. To account for differences in biodegradation rate between different top-selling drugs, a 'time resolved' PEC/PNEC equation is introduced. If the substance was classified in fass.se as '*Ready biodegradable*' (it passes the OECD 301 test) a small fraction, 10 % of the sold amount, is assumed to be present in the environment after 12 months. This corresponds to a linear degradation rate, independent of concentration, of 17.5%, degradation/month (or a system DT50 of 3.6 months). If the substance was classified in fass.se as '*Inherently biodegradable*' (it passes the OECD 302 test) a small fraction, 20 %, of the sold amount, is assumed to be present in the environment after 12 months. This corresponds to a linear degradation rate, independent of concentration, of 12.6 %, degradation/month (or a system DT50 of 5.17 months). Furthermore, if a substance possesses biodegradation data on fass.se such as "failed" OECD 301/302 data and/or abiotic degradation data that support the notion of degradation, albeit very slow, the fraction of the sold amount still remaining in the environment after 12 months is assumed to be 40 %. This class has been assigned the title "Slowly degradable" and the assumed degradation rate corresponds to 7.4 % degradation/month (or a system DT50 of 9.1 months). Finally, when persistence data is lacking altogether in the fass.se database, or when degradation tests suggests 0 % degradation in OECD 301/302 systems, the fraction of the sold amount still remaining in the environment after 12 months was assumed to be 80 % (this corresponds to a degradation rate of 1.8 % degradation/month or a system DT50 of 37.3 months). The last class was entitled "Persistent".

For all classes of relative persistence proposed herein, the environmental concentration of the pharmaceuticals (in the aquatic environment in

the Nordic countries) is such that 0<sup>th</sup> order degradation kinetics prevails. When a reaction is of 0<sup>th</sup> order the reaction kinetics are independent on the starting concentration. Assuming 0<sup>th</sup> order kinetics is of course scientifically controversial to defend. However, since the time period under study, a decade, is rather short it would be difficult, from the persistence data currently available, to assign any other type of degradation pattern.

By also imposing data on the persistence in the PEC/PNEC quotients it will in fact be possible to account for concentration build-up for some of the drugs being environmentally compared in the study. It must be stressed however that the time-resolved PEC/PNECs (taking persistence into consideration) should not mixed up with the standard PEC/PNECs also presented herein, and that this novel methodology of doing environmental risk assessment needs to be supported by extensive measurements before any decisive conclusions can be drawn from the time resolved PEC/PNEC-quotients.

## 2.9 Pharmaceuticals without PNECs

### *Read-across and grouping*

Read-across of hazard data between structurally related substances is well accepted by some regulatory authorities. The authorities in the UK, for instance, advocate that if at least the acute oral toxicity and an Ames test are available for both substances, read-across of toxicological data can be used as support for decision making in environmental risk assessment in general. In the formal market registration process of a pharmaceutical, read-across is not supported by EMEA. However, in the light of missing ecotoxicological data and in the perspective of this work with the retrospective risk assessment of pharmaceuticals in the Nordic countries, read-across has been applied rather than using quantitative structure activity relationships (QSARs). Since there are not yet any available QSAR models dedicated to predict the ecotoxicological properties of pharmaceuticals (with any accompanying uncertainty assessment), read-across, utilised with caution seems to be a more rational methodology.

The successful read-across of data requires similarity in the two substances of:

- purity/impurity profiles, as small amounts of impurities can lead to large differences in toxicology
- physico-chemical properties, particularly physical form, molecular weight, water solubility, partition coefficient and vapour pressure, as these strongly affect the bioavailability of the substance
- toxicokinetics, including metabolic pathways, although this is difficult to predict

Read-across, of course, can only be successful if good quality data is available for the known substance. Chemical grouping (or category formation) is similar in principle to read-across, but involves proposing a group of structurally related chemicals in which data on a few of the members can be shared amongst the whole group. Industry benefit from reduced testing times and costs compared with testing of each individual member of the group, particularly through fewer repeat-dose toxicity tests. Substances in a group have similar or predictably variable structural features, physico-chemical and/or toxicological properties. The group may have one or more of the following features:

- a common functional group, e.g. a ketone
- similar breakdown or metabolic products, e.g. hydrolysis of esters; or oxidation of primary alcohols and aldehydes to carboxylic acids
- incremental change across a group, e.g. carbon chain length

Once the membership of the group has been proposed, the user should use available information to check the coherence of the group, and establish the rules for inclusion or exclusion from the group (the applicability domain), with a view to maximising the size of the group. Grouping has a tendency to over-classify, so the proposer should take care in including in a group any substances where the classification has a large commercial impact. The members at the edge of the group are tested, because the authorities prefer interpolation of results within a group, rather than extrapolation.

## 3 Results and discussion

In this chapter the environmental risks associated with the consumption levels of human pharmaceuticals in the Nordic countries are displayed and analysed. First, a brief presentation of the data from each country is given; how does the sales and prescripational pattern of each country deviate from the “Nordic norm“, are data subdivided between primary and secondary sales, which type of drugs represents the highest usage, which type of drugs represents the highest number of kilograms of active ingredient sold (and thereby the highest PEC-value), which type of drugs represents the highest environmental risk (PEC/PNEC), and subsequently which type of drugs possess the highest accumulated environmental risk (PEC/PNEC-acc., for the period 1997–2007)?

In a subsection to these data and the country-specific analysis, an in-depth analysis of several active substances working on the same human target receptor or protein is presented. This type of analysis is limited to drugs of certain ATC-groups (4th level ATC-codes) such as the drugs from the ATC group N06AB (selective serotonin re-uptake inhibitors). Another example of such receptor groups are the proton pump inhibitors (PPIs), all possessing the action of selective binding to the gastric proton pump motor; the gastric H<sup>+</sup>/K<sup>+</sup> ATPase proteins. Gastric ATPase proteins are only expressed by organisms having a “stomach“ of some kind, whereas the analogue protein family of vacuolar ATPases are expressed by virtually all eukaryotic cell types. Furthermore, the vacuolar type H<sup>+</sup>-ATPase (V-ATPase) is an evolutionary conserved enzyme with remarkably diverse functions in eukaryotic organisms. V-ATPases acidify a wide array of intracellular organelles and pump protons across the plasma membranes of numerous cell types. V-ATPases couple the energy of ATP hydrolysis to proton transport across intracellular and plasma membranes of eukaryotic cells. Human drugs targeting the gastric H<sup>+</sup>/K<sup>+</sup> ATPase proteins are thus relevant to risk assessors as a group of substances possibly also affecting other species in the environment.

The ATC-groups G03AA, G03AB, G03C, G03FA, G03FB, all actively targeting the human oestrogen receptor (a DNA binding transcription factor which regulates gene expression of a large number of proteins) is of course highly interesting to evaluate in terms of the total estrogenic and toxic load, and corresponding environmental risk. Albeit, the exact mechanism of action these drugs is not the scope of this study. However, it has been concluded in several experimental studies that many organisms such as fish and amphibians possess ER-receptors similar to those found in humans. These species can thus be accepted to be affected by the estrogenic drugs in very much the same manner as humans would.

From an environmental risk assessment perspective, all drugs targeting the same receptor or receptor family should be assessed together. This would of course result in a very conservative risk assessment since not all drugs targeting the same receptor or receptor family would necessarily distribute in a similar pattern in the environment. Also, differences in metabolic profile (type and potency of metabolites) will affect the environmental impact of drugs targeting the same receptors. Since several of these parameters needed for a fully parameterised risk model of estrogenic compounds are still unknown, the environmental risk has been elaborated on for each compound separately but with an attempt to include all possible formulations in the assessment.

Also, with regard to the consumption levels (*i.e.*, sales levels) of sex hormones (estrogens) in the Nordic countries it should also be taken into consideration that several of the hormone substances are endogenously being excreted also from persons that do not eat estrogen hormone-containing medicine. Thus, the contributions from endogenously produced estrogens among a population may outnumber the estrogen load from the consumption of contraceptive pills and hormone replacement therapy by several orders of magnitude. The relationship between naturally produced (and hence excreted) hormones and excretion of hormones from medical treatment of any kind has been scrutinized by Johnson et al (Johnson et al., 2000 and 2004) attempting to develop a semi-quantitative model for the predication of STP influent concentrations of estrogens. Even though the work by Johnson et al is largely based on a wide variety of assumptions (combined with pharmacokinetic data for ethinyl estradiol and estradiol) it has been made probable that the estrone load (estrone being both a metabolite and a transformation product of estradiol) to municipal STPs can be subdivided into 30–35 % stemming of the excretion from pregnant women (thus an endogenous source), 20–30 % from menstrual women (thus another endogenous source), 5–10 % from males (thus another endogenous source), 1–5 % from menopausal women (yet another endogenous source), 5–10 % from females on hormone replacement therapy (an exogenous source), and some 20–30 % from the conversion of estradiol in the sewers (will be a composite of endogenous and exogenous sources). Thus, with regard to estradiol at least 75 % of the load to the STPs could stem from endogenous sources.

With regard to ethinyl estradiol (EE2), the whole load reaching a municipal STP is of course stemming from the consumption of contraceptives. In reality ethinyl estradiol is excreted mainly in different forms of conjugates (glucuronides, sulphates) and phase 1-metabolites (hydroxy- and methoxy-variants). However, the model by Johnson et al (2004) suggests that ethinyl estradiol primarily reaches the municipal STPs in form of glucuronide conjugates (30 % of the EE2 load in faeces and 63% of the EE2 load in urine). Since the model of EE2-excretion and the fate of the different metabolites and conjugates of EE2 in the STP are largely

unknown this study has conservatively judged the environmental risks associated with EE2 based on the assumption that the total consumption reaches the aquatic environment as EE2 (no metabolism accounted for).

For some countries such as Sweden and Norway, the project study could not access sales data from all consecutive years in the period 1997–2007, but every second year or so. In those cases, a simple linear interpolation has been performed in order to retrieve a 'full' dataset for the purpose of graph plotting.

Regarding the National PEC-values over the whole period, PECs for almost all drugs sold can be calculated. However, the assignment of this project limited the number of pharmaceuticals to 20–30 (the top-selling drugs). A practical approach to the limit value regarding PECs, is to plot all PEC-values that could correspond to measured environmental concentrations above the analysis method LODs (normally 1–50 ng/l in surface water). It seems of less concern to display and discuss PEC-values below any chemical analysis LOD.

The PECs as well as the PEC/PNECs are constantly being plotted in a segmented group-wise pattern for optimal resolution in the figures. Normally the interesting drugs sold in a country are sub-divided into 3–4 figures.

Due to difficulties with the risk assessment and sales assessment of ketoconazole, all data regarding that substance were selected for an in-depth study, presented in chapter 4.

### 3.1 Sales and Consumption in Denmark 1997–2007

Sales data from Denmark constituted both primary sales (from pharmacies to private customer) as well as secondary sales (from hospital pharmacies to hospital wards- 'stockist to retailers'). Since data from all years during the period were accessible to the project, the Danish data constitute maximal resolution.

A visual basic macro routine enabled the selection of the top-40 human pharmaceuticals (in terms of sold DDDs) out of a list of basically all pharmaceuticals sold during the period. Data were subdivided between primary and secondary sales.

Out of the top-40 list one drug stood out as different in terms of the consumption-prescription pattern; prednisolone (H02AB06). In the case of prednisolone the fraction used at hospitals was between 7 and 18 % of the total annual sales during the period 1997–2007. For all other top 40 drugs in Denmark the fraction used in hospitals (and subsequently being excreted into hospital sewers) was between 1 to 4 %.

Prednisolone is a corticosteroid drug with predominantly glucocorticoid activity, making it useful for the treatment of a wide range of inflammatory and auto-immune conditions such as asthma, uveitis, rheuma-

toid arthritis, ulcerative colitis and Crohn's disease, multiple sclerosis, cluster headaches and Systemic Lupus Erythematosus. It can also be used as an immunosuppressive drug for organ transplants and in cases of adrenal insufficiency.

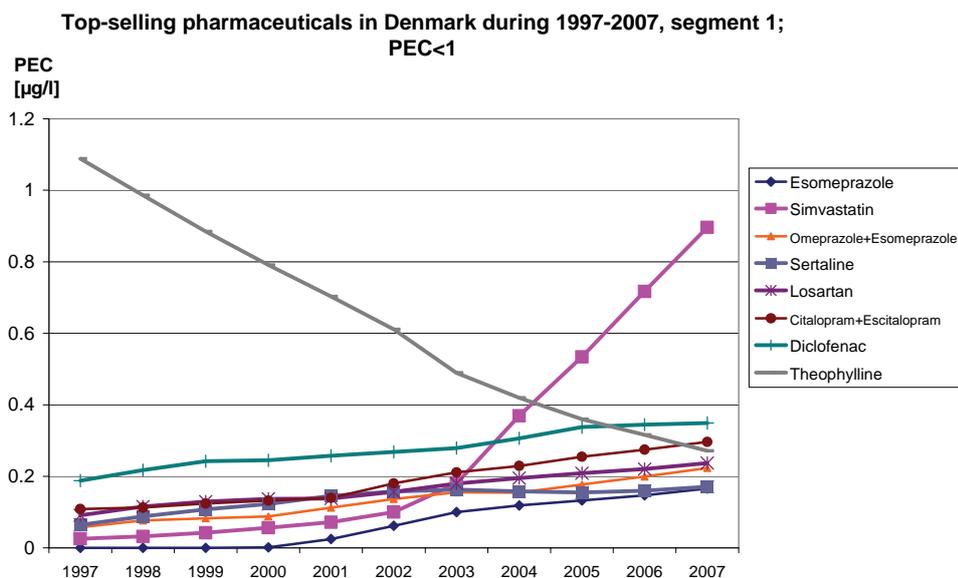


Figure 3. Data represents the PEC values of drugs having median-PECs < 1 µg/l during 1997–2007.

Regarding the top 40-drugs in Denmark during the period the corresponding PEC-values (from Eq. 1) will be presented in three different figures depending on the median PEC during the period; Figure 3; median-PEC < 1, Figure 4; 1 < median PEC < 5, and subsequently Figure 5; median PEC > 5.

From Figure 3 it is interesting to note that the sales of the Hypolipidemic agent simvastatin (it is used to control hypercholesterolemia elevated cholesterol levels and to prevent cardiovascular disease) is rapidly increasing from 2002 and onwards (sales increased by 3416 % from 1997–2007), whereas the sales of the drug theophylline (a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease and asthma) decreases throughout the period (-75 % decrease in sales from 1997–2007). These two stand out as deviators from the general pattern of a steady increase in sales (and thus in environmental risk) by roughly 85–287 %.

Sales of esomeprazole (a proton pump inhibitor and one enantiomer of the racemate omeprazole) increased by 14 000 % during period 2000–2007 due to market approval in 2000 and hence no prior sales. Similarly escitalopram (SSRI drug and an enantiomer to the racemate citalopram) experiences a 3 700 % increase in sales between 2002 and 2007 (market approval in 2002).

### Top-selling pharmaceuticals in Denmark during 1997-2007, segment 2; $1 < \text{PEC} < 5$

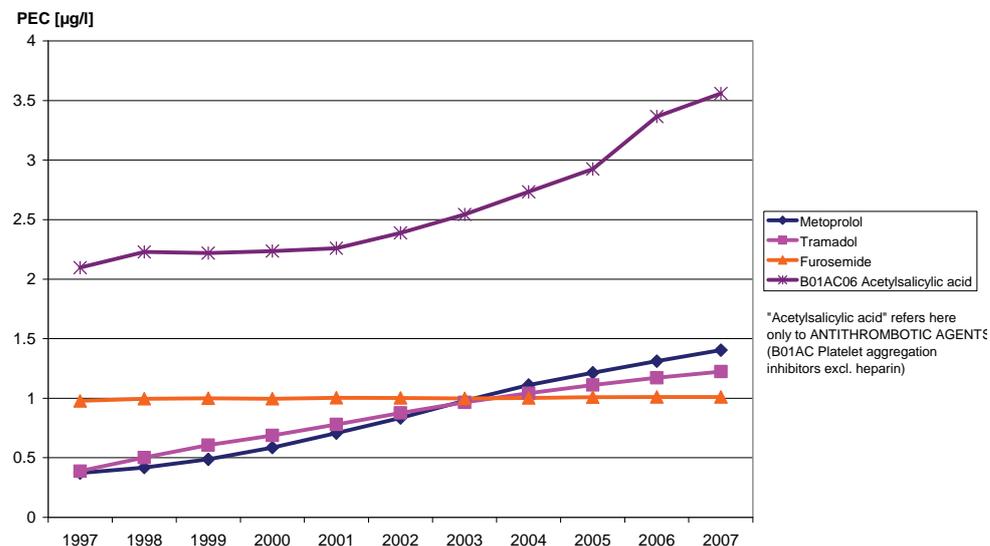


Figure 4. Data represents the PEC values of drugs having median-PECs between 1 – 5 µg/l during 1997–2007.

In the next segment of top-selling drugs in Denmark during the period (Figure 4) (drugs with exceedingly low PECs,  $\text{PEC} < 0.01$ , have not been included in plots regardless of a top-40 position since current limits of detection in analytical methods would hardly detect them) furosemide (a loop diuretic used in the treatment of congestive heart failure and oedema) stands out as vastly different since the sales are practically unchanged throughout the period (min PEC 0.98 µg/l, max PEC 1.01 µg/l). Tramadol (a centrally acting analgesic opioid) and the  $\beta$ -blocker Metoprolol experiences a similar increase in the sales during the period, 215 and 278 % increase respectively.

The highest PEC-values noted in this segment refer to the ATC-group B01AC06 of acetylsalicylic acid in which only the fraction of acetylsalicylic acid being sold as an antiplatelet drug (a class of pharmaceuticals that decreases platelet aggregation and inhibits thrombus formation) are included.

### Top-selling pharmaceuticals in Denmark during 1997-2007, segment 3; PEC<5

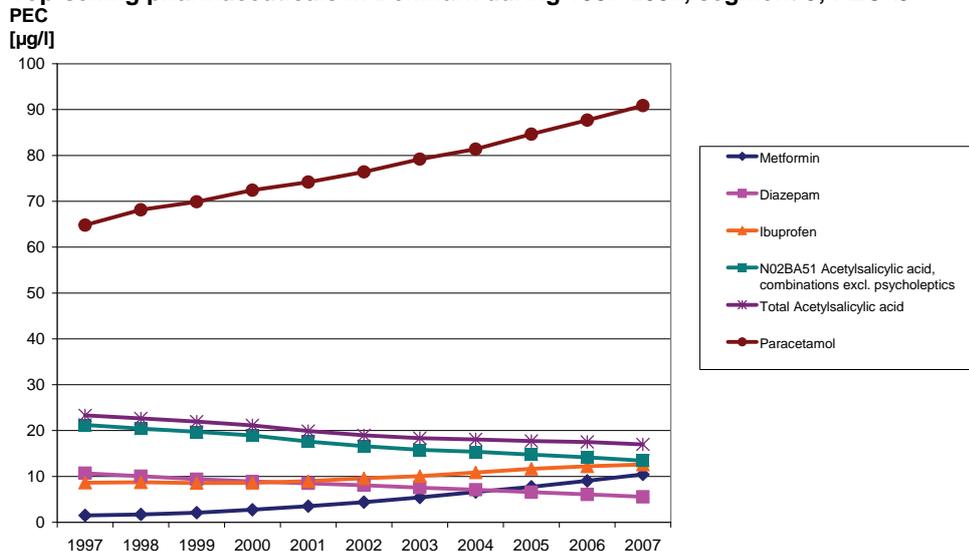


Figure 5. Data represents the PEC values of drugs having median-PECs exceeding 5 µg/l during 1997–2007.

Amongst the top-selling five drugs in Denmark during the period the well known analgesic paracetamol had annual sales of 26–36 tonnes (median 31 tonnes). PEC-values of 65–90 µg/l are of course highly unrealistic (Figure 5). However, paracetamol have been reported to be “slowly degraded in the environment” and can thus not be expected to biodegrade at a significant rate in the WWTPs. There are studies indicating a very high removal rate of paracetamol in modern three-stage WWTPs (removal of 90–95 % have been reported). Applying such removal efficiencies (Ternes et al., 1998, as well as Landstinget i Uppsala län, 2005), and assuming that all consumers of the pharmaceutical live in urban areas with full affiliation to the local WWTP, a median PEC for the period would be 0.3 µg/l, thus a substantial decrease.

As for the other drugs in Figure 5, ibuprofen the NSAID drug, shows a slight increase in sales and in corresponding predicted environmental concentration (a 45 % increase between 1997 and 2007). Also in this case the corresponding PEC value may be the subject to refinement. Studies indicate an average removal of ibuprofen of 70% in modern WWTPs. Employing such figures (Anderson and Woldegiorgis et al., 2006) the mitigated Danish median-PEC of ibuprofen would be 2.9 µg/l during the period. Another increasingly used drug is the oral anti-diabetic drug metformin with a 600 % increase in the sales during the period. Since metformin has a reported biodegradation rate of “Ready biodegradation = 0.6% in 28 day (OECD 301)“, it is rather ambiguous as to whether the PEC value can be reduced by incorporating mitigating effects from WWTP removal. The other pharmaceuticals in this figure; diazepam (the benzodiazepine having anxiolytic, anticonvulsant, sedative, skeletal muscle relax-

ant and amnesic properties) as well as the two listed variants of acetylsalicylic acid show decreased sales 47, 38 and 27 % decrease respectively.

### 3.2 Environmental risks in Denmark 1997–2007

In order to assess whether the listed consumption levels in Denmark 1997–2007 pose any environmental risk, consumption of each pharmaceutical resulting in a predicted environmental concentration, is compared with the highest tolerable concentration of that pharmaceutical, without affecting any aquatic species living there; the Predicted No Effect Concentration (the PNEC-value).

Most PNEC-data used herein stems from data publicly available at the website [www.fass.se](http://www.fass.se). Such data are voluntarily being submitted to the fass-system by pharmaceutical companies worldwide. The overwhelming majority of the ecotoxicological data in fass.se originate from the testing procedure preceding market approval, and are conducted in accordance with EMEA or OECD standard protocols.

In a similar fashion as for the Danish consumption data, the PEC/PNEC data is displayed in four different plots, spanning different PEC/PNEC-regions.

Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, segment 1; PEC/PNEC<0.1

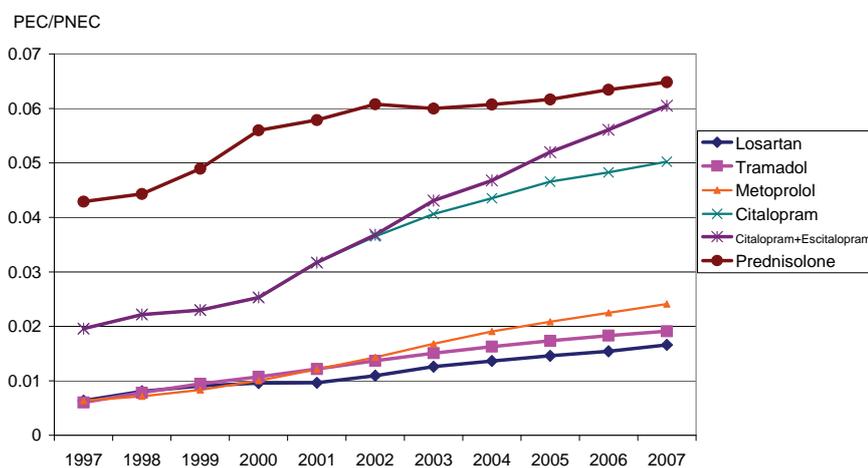


Figure 6. Data represents the environmental risks in Denmark associated with drugs having low PEC/PNEC-ratios during 1997–2007.

In the first risk quotient plot (Figure 6), pharmaceuticals having a median PEC/PNEC-quotient <0.1 are included. For all drugs in this particular group it is evident that the increased consumptions are reflected in increasing risk quotients. The averaged increase over the period for these six drugs is 178 %. Regarding the SSRI drugs citalopram and its enantiomeric counterpart escitalopram, the common PNEC value of 4.9 µg/l

stems from a 48 hr EC<sub>50</sub> test on the calanoid copepod *Acartia tonsa*. The most rapidly increasing drug in this risk quotient-region is citalopram/escitalopram. However, if the PNEC value used in this particular case is considered reliable, the summed consumption of citalopram/escitalopram may increase at this rate for another 215 years before reaching any environmental risks (PEC/PNEC>1). As for the other drugs in this risk quotient-region, consumption could steadily increase for even further prior to any apprehensible risk to occur.

Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, segment 2;  
0.1<PEC/PNEC<0.5

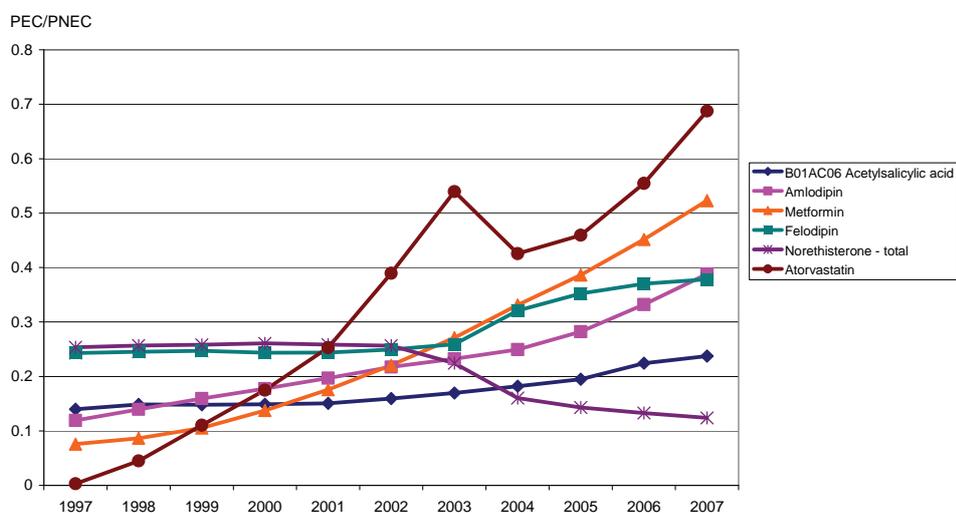


Figure 7. Data represents the environmental risks in Denmark associated with drugs having medium PEC/PNEC-ratios during 1997–2007.

In the second PEC/PNEC-quotient figure (Figure 7), disseminating the drugs having a median risk quotient of  $0.1 < \text{PEC/PNEC} < 0.5$  several of which show an increased risk over the time period studied. Norethisterone, the androgenic hormone usually used in contraceptive pills, contrary to the others, show a decreasing trend from a PEC/PNEC of 0.26 to a PEC/PNEC of 0.13 at the end of the time period. Norethisterone, like all progestagens, have antiestrogenic properties thus counteracting the effects of estrogens in the organism, as well as being antigonadotropic, i.e., inhibiting the production of sex steroids by gonads. The decrease in the consumption (and thus the risk) could possibly stem from an increased use of third-generation oral contraceptives utilising other progestagens to balance side-effects of ethinyl estradiol. Within the Danish dataset it is very difficult indeed to accurately assess the total sales of norethisterone since several ATC-groups do not possess well defined daily doses (DDDs) for instance gels, dermal patches, vagitories etc. In those cases “project-specific” daily doses, based on the amount of active ingredient per unit dose (the UD) has been calculated for a number of products on the market containing the substance, as specified in the prescriber’s guidance to

Swedish doctors. These figures have then been used also for Denmark, Finland, Norway and Iceland.

In the case of norethisterone the calculated consumption in ATC groups G03FA01 (norethisterone and estradiol), G03FB05 (norethisterone and estradiol) and G03AA11 (Norgestimate and ethinyl estradiol) have been added up each year. Norgestimate is not exactly the same substance as norethisterone but a structural analogue targeting the very same receptors.

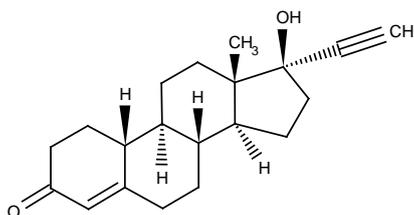


Figure 8. Norethisterone, CAS 68-22-4.

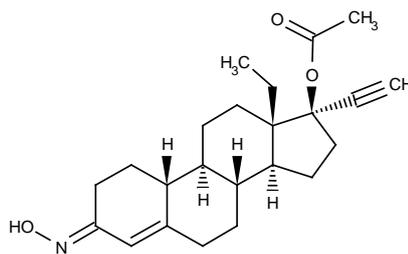


Figure 9. Norgestimate, CAS 35189-28-7.

G03FA01 – (norethisterone and estradiol), normally the pills contain 1 mg of estradiol and 0.5 mg of norethisterone, a packet contains 28 tablets and should be dispensed one each day. Thus, the project specific DDD for G03FA01 (norethisterone) equals 0.5 mg/day, and the corresponding value for estradiol is 1 mg/day.

The amounts of norethisterone consumed in ATC-groups G03FB05 (and G03AA11) are very much calculated in the same manner.

Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, segment 3;  $0.5 < \text{PEC/PNEC} < 3$

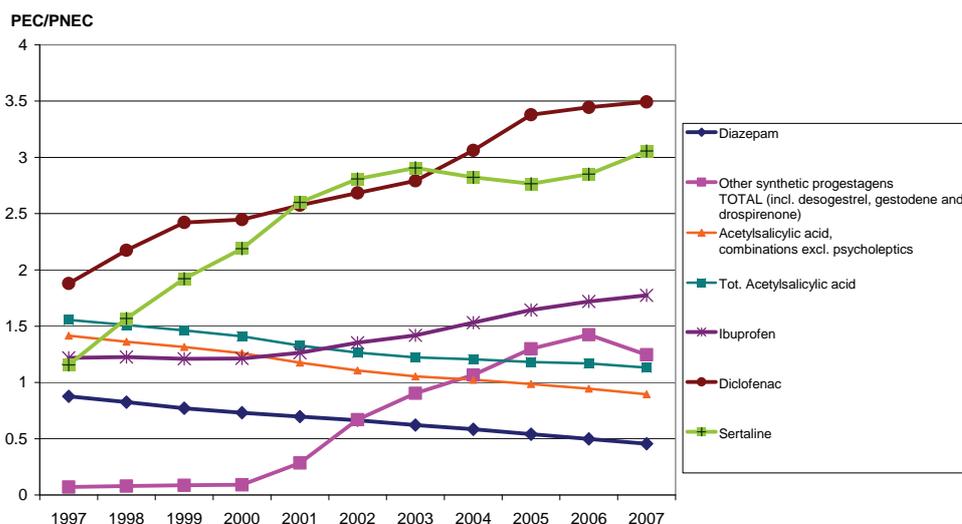


Figure 10. Data represents the environmental risks associated with drugs having medium-to high PEC/PNEC-ratios during 1997–2007.

In the next figure (figure 10), drugs having median risk quotients of  $0.5 < \text{PEC/PNEC} < 3$  are displayed. In this category, the current consumption is most definitely causing environmental risks for aquatic organisms and eco systems. Sertraline and diclofenac seems to be of equal concern having current PEC/PNEC quotients of 3–3.5. Also, diclofenac, notoriously known to pass modern WWTPs with virtually no losses to absorption nor to biodegradation, thus will the amounts consumed eventually reach the water recipients (Andersson et al., 2006). Ibuprofen is enlisted in

Figure 10 as having a PEC/PNEC exceeding 1 (thus, with an environmental risk), however the data have not been corrected for removal in the WWTPs. Correcting these PEC/PNECs for ibuprofen with WWTP-removal would still render ibuprofen a period median value of 0.4.

The progestagens (desogestrel, gestodene and drospirenone) are structural analogues but not identical. Since no ecotoxicological data could be retrieved for these substances and QSAR modelling would be rather error prone, the PNEC of these substances was assumed to be equal to that of norethisterone ( $0.01 \mu\text{g/l}$ ). All three anti-estrogens are used in contraceptives to counteract and balance the negative side effects of ethinyl estradiol. Similar to the situation with norethisterone, project-specific DDDs were calculated also for this particular group of substances. For instance, in ATC-group G03AA12 a typical product contains 3 mg drospirenone and 3  $\mu\text{g}$  ethinyl estradiol, and a typical “course of treatment” contains 21 tablets with the above compositions and 7 “dummy” tablets. Thus the DDD of drospirenone would then be equal to  $3 \cdot 21 / 28 = 2.25 \text{ mg/day}$ .

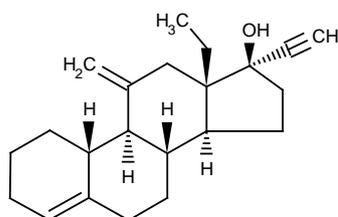


Figure 11. Desogestrel, CAS 54024-22-5

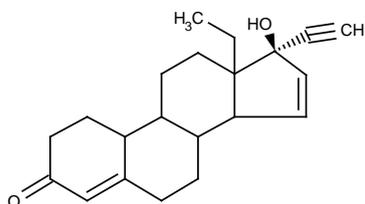


Figure 12. Gestodene, CAS 60282-87-3

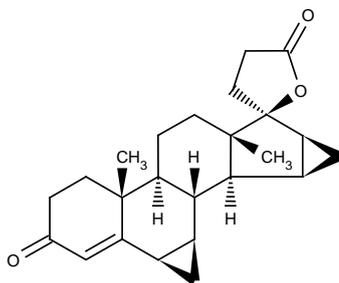


Figure 13. Drospirenone, CAS 67392-87-4

**Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, segment 4; PEC/PNEC>3**

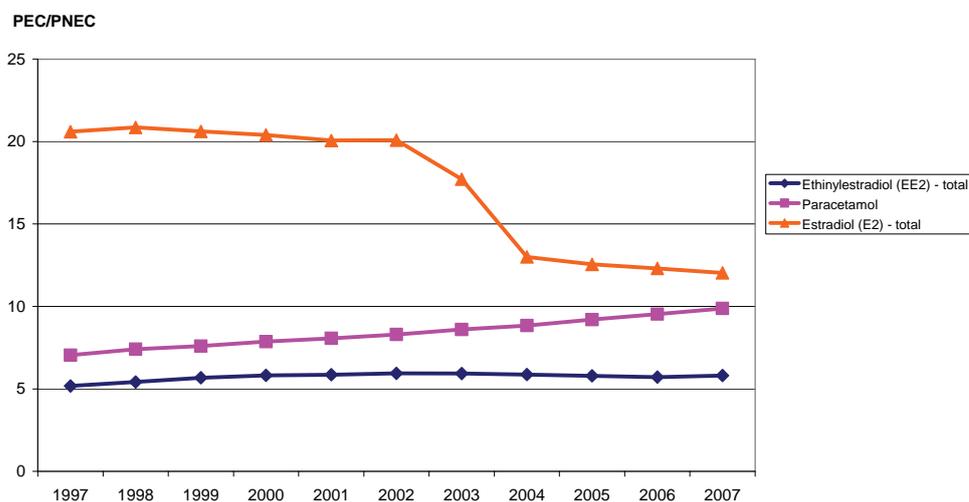


Figure 14. Data represents the environmental risks associated with drugs having high PEC/PNEC-ratios during 1997–2007.

In the segment of human pharmaceuticals sold in Denmark having the highest environmental risks (median PEC/PNEC during the period > 3, (Figure 14) the analgesic paracetamol as well as two estrogenic hormones; estradiol and ethinyl estradiol. Both of these substances encompass several ATC-groups and administration forms (oral tablets, vagitories, dermal patches, gels etc.) and for some of the variants it is very difficult to assess the size of a DDD. For instance, in the ATC group G03CA03 on the Swedish market encompasses the following administrative routes and corresponding “DDDs” (50 µg-5 mg);

- G03CA03 Estradiol 0.3 mg N (N = nasal)
- G03CA03 Estradiol 2 mg O (O = oral)
- G03CA03 Estradiol 1 mg P depot short duration (P = parenteral)
- G03CA03 Estradiol 0.3 mg P depot long duration
- G03CA03 Estradiol 5 mg R (R = rectal)

- G03CA03 Estradiol 50 µg TD patch refer to amount delivered per 24 hours
- G03CA03 Estradiol 1 mg TD gel (TD = transdermal)
- G03CA03 Estradiol 25 µg V (V = vaginal)
- G03CA03 Estradiol 7.5 µg V Vaginal ring refers to amount delivered per 24 hours.

In order to be able to include all these different formulations, the project decided to use a DDD of 2.5 mg as a worst case scenario. This DDD could very well be an overestimation. However, regarding the estradiol counterpart of ATC G03FB05 (“Progestogens and estrogens, sequential preparations”), the daily doses of estradiol based on the UD-concept previously depicted (“active ingredient per unit dose”) varied between 1-50 mg, and for the purpose of this project, a DDD of 2 mg was chosen (partially counterbalancing the DDD of 2.5 mg in G03CA03).

The estrogens tend to end up amongst the drugs having a very high environmental risk in all compilations of risk and hazards of pharmaceuticals, presumably due to the very low effect concentrations that triggers response in fish and amphibian species when tested for chronic toxicity.

Paracetamol is not very toxic by any standard but the overall consumption of 260–264 tonnes annually during the period 1997–2007 in Denmark results in a high environmental risk.

As for the estrogens, WWTPs having biological nitrogen removal technology generally removes 50–70 % of the incoming flux of these substances. Thus, the median PEC/PNECs might as well be a factor of two lower than depicted in the figure (Figure 14). On the other hand, the estradiol mass load in the WWTP-influents also receives a substantial contribution from the endogenously excreted fraction (men and women naturally excrete the substance at very varying concentrations during the course of life).

### 3.3 Accumulated environmental risk in Denmark 1997–2007

Throughout the decade studied (1997–2007), the environmental risk assessments have been estimated annually, with the underlying assumption that the environmental concentrations are being “zero-adjusted” on New Year's Eve every year, i.e., the risk assessment procedure does not take into consideration that continuous inflow of persistent chemicals into the environment might in fact cause concentration build-up. In an attempt to take the potential to resist biodegradation (and hence have the propensity to concentration build-up) an alternative PEC/PNEC-calculation is presented herein where biodegradation data from [www.fass.se](http://www.fass.se) has been util-

used to assess the accumulative PEC/PNEC quotients (the theory behind this is described in Ch. 2.8).

The accumulated PEC/PNECs are being presented in two consecutive figures, depending on the numerical outcome.

Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, with respect to the reported biodegradation rates, segment 1;  $0.51 < \text{PEC/PNEC} < 3$

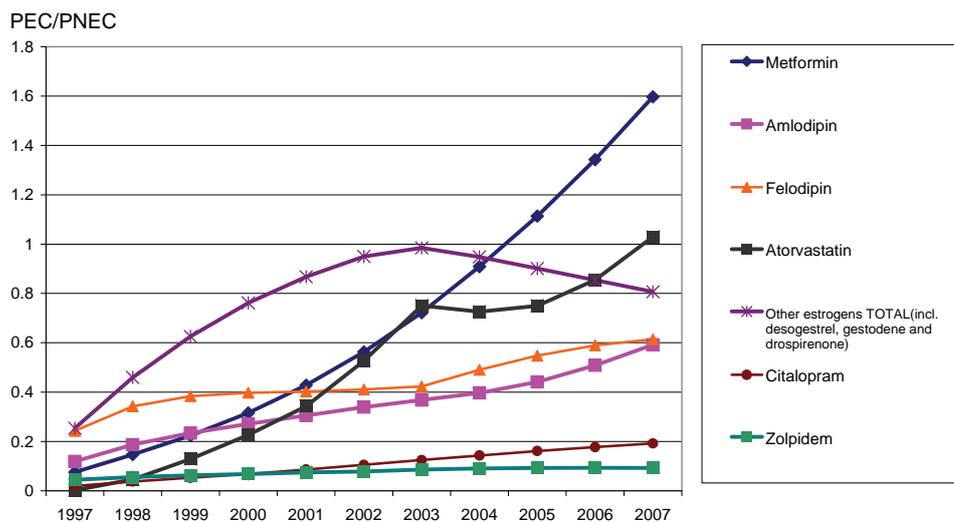


Figure 15. Data represents the accumulated environmental risks in Denmark associated with drugs having low PEC/PNEC-ratios in combination with medium persistence, during 1997–2007.

In Figure 15, drugs which will increase their environmental risks into the significant risk region ( $\text{PEC/PNEC} > 1$ ) during the period (due to low biodegradation rates) are displayed.

The anti-diabetic drug metformin had an initial 1997 PEC/PNEC of 0.076 reflecting a low or even insignificant environmental risk. A decade later, accumulation due to slow biodegradation, renders a 1997–2007 accumulated PEC/PNEC of 1.6.

Atorvastatin, a member of the drug class known as statins (used for lowering blood cholesterol), shows a steep accumulation but discontinuous profile going from a 1997 PEC/PNEC of 0.003, through a decade of continuous accumulation (40% of the consumption each year is believed to remain due to the class “..slowly degraded in the environment”), to a final 1997–2007 accumulated PEC/PNEC of 1.03. A similar type of accumulation slopes can be identified for the long-acting calcium channel blocker amlodipine (used as an anti-hypertensive and in the treatment of angina), going from a 1997 PEC/PNEC of 0.12 to an accumulated 1997–2007 PEC/PNEC of 0.59. The analogue felodipine (also a long-acting calcium channel blocker) has an initial 1997 PEC/PNEC of 0.24 then 40% of annual consumption is being considered as remnants each year, leading to a accumulated 2007 PEC/PNEC of 0.61.

**Top of the PEC/PNEC-list for pharmaceuticals in Denmark during 1997-2007, with respect to the reported biodegradation rates, segment 1; PEC/PNEC > 3**

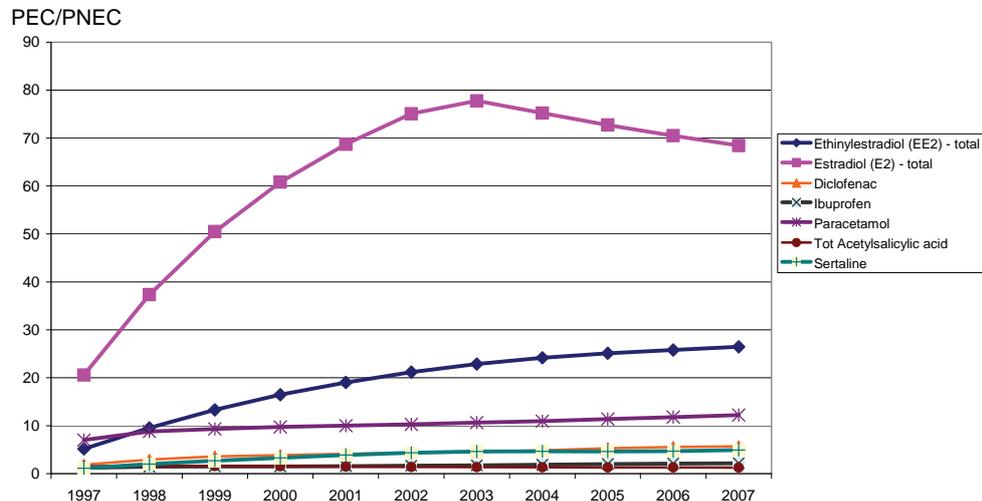


Figure 16. Data represents the accumulated environmental risks associated with drugs having high PEC/PNEC-ratios in combination with medium-high persistence, during 1997–2007.

In Figure 16, drugs having higher PEC/PNEC-quotients, combined with higher persistence according to biodegradation tests are displayed. Estradiol and ethinyl estradiol, both classified as potentially persistent have high PEC/PNEC-quotients in 1997 (20.6 and 5.2 respectively). A decade later, with an 80 % of each annual load being accumulated, the 1997–2007 PEC/PNEC become 68.5 and 26.5 respectively.

This is probably a worst case scenario but still clearly illustrates how the situation could drastically deteriorate in a small recipient receiving effluent water from a normal WWTP, where dilution factor is ten or less. This accumulation data might actually reflect the situation fairly well in countries with cold climates, such as the Nordic countries. As for the other high PEC/PNEC-drugs, acetylsalicylic acid is probably “ready biodegradable”, having a recorded 100% biodegradation in 14 days in an “ISO TC/147, SC5/WG4, N141 BOD-test for Insoluble Substances”. This renders an accumulation of only 10 % annually, and hence the PEC/PNECs remain virtually constant, reflecting only changes in consumption. Also paracetamol and ibuprofen (both classified as inherently biodegradable, 20 % annual accumulation), and sertraline and diclofenac (slowly degraded, 40 % annual accumulation) reflect small changes in the accumulated 1997–2007 environmental risks.

### 3.4 Sales and consumption in Finland 1997–2007

The Finnish data consisted of sales data from all years during the period. From the raw data files it was difficult to assess whether all formulations were included. Doubts can be raised about the completeness of data especially regarding the ATC-group G03 Sex hormones. A list of formulations containing estrogens and anti-estrogens were not included in the Finnish data set. Whether these formulations are absent from the Finnish market during the period is still unclear;

G03FA15, G03FB05, G03FB06, G03FB09, G03AC01, G03AC08, G03AC09, G03AB04, G03AA11, G03AA05, G03AA07, G03AA09, G03AB03, G03CA03, G03CA04, G03FA01.

These types of pharmaceuticals were sold in Denmark and Sweden during the period.

The Finnish data were not subdivided between primary and secondary sales and hence no estimate of the contribution to the environmental load from hospitals could be made.

A visual basic macro routine enabled the selection of the top-100 ATC-codes of human pharmaceuticals (in terms of sold DDDs) out of a list of basically all pharmaceuticals sold during the period. The top-100-list constituted approximately 65 different active substances out of which 34 different substances were selected for PEC-calculation and environmental risk assessment.

Regarding the top 34- drugs in Finland during the period the corresponding PEC-values (from Eq. 1) will be presented in five different figures depending on the median PEC during the period; Figure 17; median-PEC<1, Figure 18; 1<median PEC<0.5, Figure 19; median PEC < 1, Figure 20; median PEC < 10, and subsequently Figure 21; median PEC > 40.

#### Top-selling pharmaceuticals in Finland during 1997-2007, segment 1; PEC<1

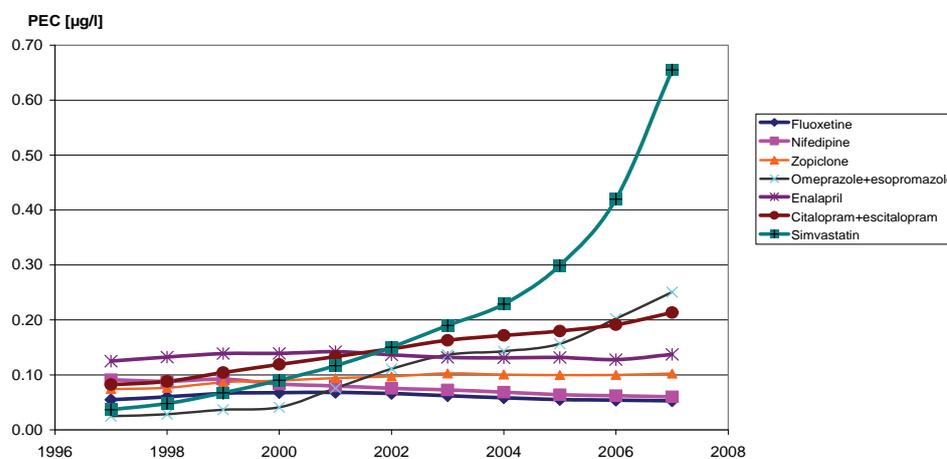


Figure 17. Data represents the PEC values of drugs sold in Finland having median-PECs below 0.7 µg/l during 1997–2007.

From Figure 17 and Figure 18 it is evident that for most of the listed pharmaceuticals in the PEC-region  $< 1 \mu\text{g/l}$ , the consumption does not seem to increase dramatically over time. All drugs present in Figure 17 may not be easily detectable if predicted and measured environmental concentrations are similar. The major exception to this pattern being simvastatin, the statin used to control hypercholesterolemia (elevated cholesterol levels) and to prevent cardiovascular disease. Sales of simvastatin increased with over 1660 % over the decade 1997–2007. However, it is very unlikely that simvastatin will ever pose any environmental risk even at higher consumption level since simvastatin is a pro-drug being readily transformed into an ionised active drug upon the first passage of the liver. The ionised active drug, the opened lactone form, is readily degraded according to data from a modified Zahn-Wellens/EMPA test (58% biodegradation after 28 days). Hydrolysis studies indicate that the ionised active compound possesses a half-life greater than one year at environmentally relevant pH and temperature. Several of the other pharmaceuticals having median PECs below  $1 \mu\text{g/l}$  during the period actually show decreasing consumption; the organic nitrate vasodilators for treating atherosclerosis and ischemic heart disease isorbid mononitrate and isorbid dinitrate. Other showing decreasing sales in Finland are the  $\beta_1$  receptor selective antagonist ( $\beta$ -blocker) Atenolol (used for treating hypertension) where sales are decreased by 50 % over the period 1997–2007. The drug triamterene (CAS 396-01-0) in Figure 18 refers to a potassium-sparing diuretic used in combination with thiazide diuretics for the treatment of hypertension and edema, in this case as one component in C03EB01 (furosemide being the other). This particular drug does not seem to be sold in Sweden or Denmark.

At the top-34 list in Finland (however at rather low PECs) two benzodiazepines are found; oxazepam and temazepam. Both these drugs are rather old (having market introduction in the late 1960's), and hence at that time environmental risk assessment was not mandatory in the registration process. Benzodiazepines possess anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. They are commonly used for treating anxiety, insomnia, seizures, alcohol withdrawal, and muscle spasms. Temazepam is not sold in Sweden and the sales in Denmark never exceed 1 kg annually.

With regard to ecotoxicological data the benzodiazepines are not well characterized and unless academic institutions undertake testing of these substances, it is highly unlikely that more data will be produced for these old substances with long-time expired patents.

## Top-selling pharmaceuticals in Finland during 1997-2007, segment 2; PEC&lt;0.5 µg/l

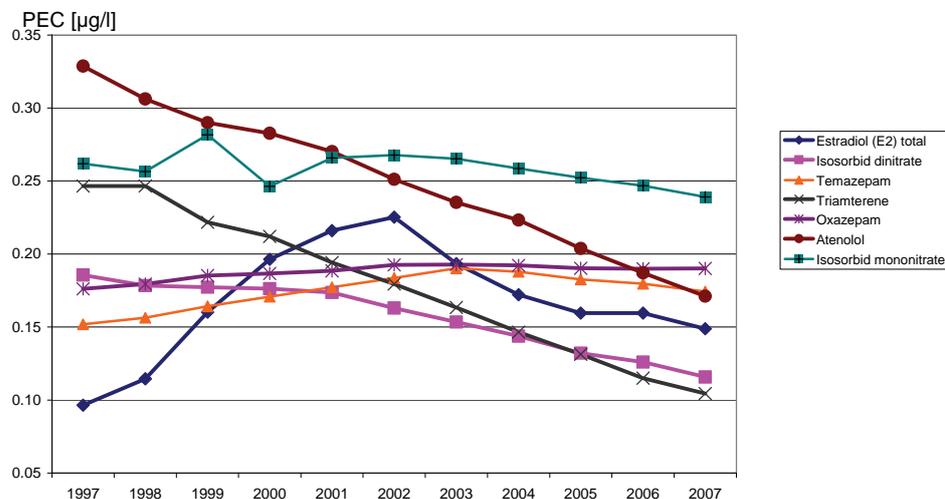


Figure 18. Data represents the PEC values of drugs sold in Finland having median-PECs below 0.5 µg/l during 1997–2007.

Since most benzodiazepines like oxazepam and temazepam have similar metabolic pathway in humans, and are being excreted as oxazepam glucuronides, it may be important for Finnish authorities to keep track of the consumption of the benzodiazepines as well as the current environmental concentrations.

There might also be another contribution to the concentrations of benzodiazepines in the Finnish environment since both temazepam and oxazepam are the most widely abused legal prescription drug in Europe, with a significant black market from smuggling (according to statistics from the Swedish Customs on seizure consignments).

## Top-selling pharmaceuticals in Finland during 1997-2007, segment 3; PEC&lt;1 µg/l

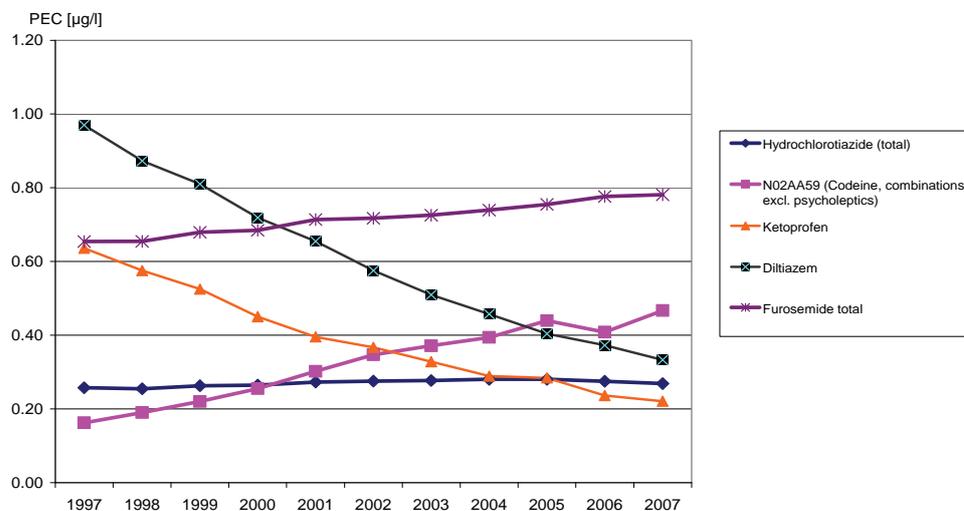


Figure 19. Data represents the PEC values of drugs sold in Finland having median-PECs below 1 µg/l during 1997–2007.

In the figure representing pharmaceuticals with median PECs just below 1 µg/l (Figure 19), most drugs show a constant (hydrochlorothiazide) and furosemide) or decreasing sales (diltiazem and ketoprofen). Ketoprofen has a somewhat higher PEC in Finland than in Sweden and Denmark, 148 kg sold in Denmark in 2007 compared with almost 900 kg sold in Finland the same year.

#### Top-selling pharmaceuticals in Finland during 1997-2007, segment 4; PEC<10 µg/l

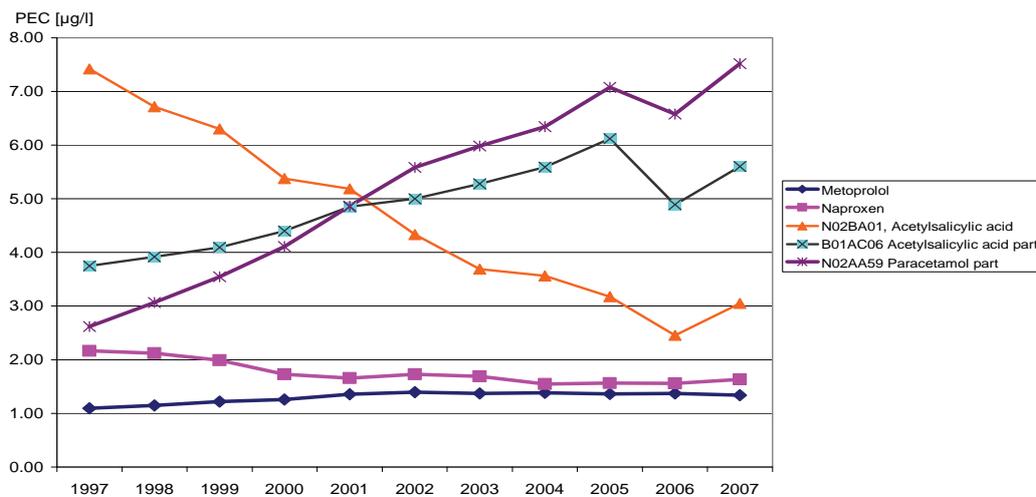


Figure 20. Data represents the PEC values of drugs sold in Finland having median-PECs below 10 µg/l during 1997–2007.

In the next PEC segment (Figure 20), showing drugs with median PEC between 1 and 10, very familiar substances appear such as the selective  $\beta_1$  receptor blocker metoprolol (used in treatment of several diseases of the cardiovascular system, especially hypertension), the NSAID drug naproxen as well as some formulations of acetylsalicylic acid (ATC N02BA01 and B01AC06, respectively) and paracetamol (ATC N02AA59 a combination with codeine).

### Top-selling pharmaceuticals in Finland during 1997-2007, segment 5; $5 < \text{PEC} < 40 \mu\text{g/l}$

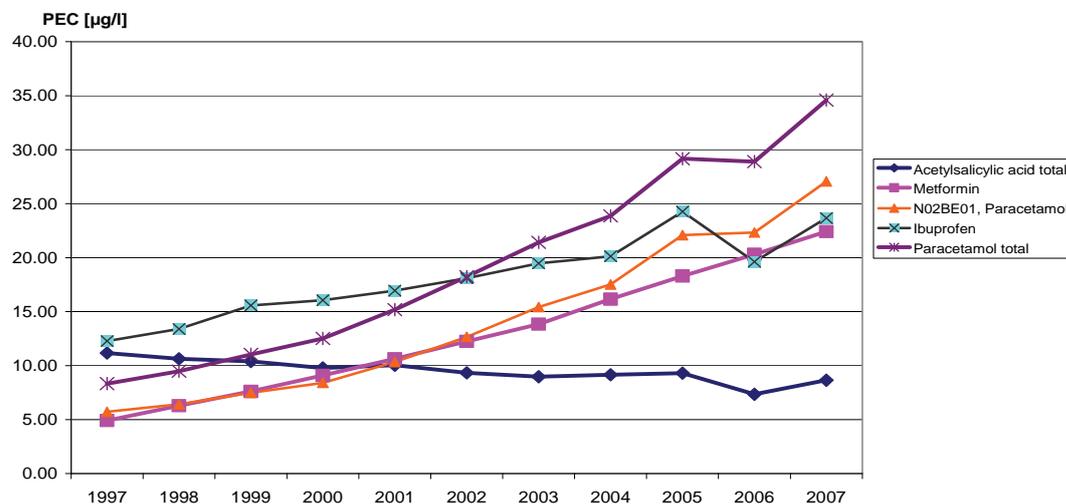


Figure 21. Data represents the PEC values of drugs sold in Finland having median-PECs below  $40 \mu\text{g/l}$  during 1997–2007.

In the last PEC-segment from Finland the real top selling formulations can be seen (Figure 21). With the exception of acetylsalicylic acid, which have declining sales in Finland, all other top selling formulations increases over time (approximately 300 % increase over the ten year period). The drugs having PECs between 5 and  $35 \mu\text{g/l}$  are acetylsalicylic acid, the anti-diabetic drug metformin, the NSAID drug ibuprofen along with the well known analgesic paracetamol (ATC N02BE01 as well as the total consumption).

### 3.5 Environmental risks in Finland 1997–2007

Altogether three different figures are used to depict the environmental risk quotients calculated for Finland. In Figure 22, the pharmaceuticals associated with the lowest ( $< 0.3$  but significant) PEC/PNEC –quotients are displayed. Furosemide, citalopram (summed together with escitalopram) and metoprolol showing a constant or slowly increasing risk pattern, while the PEC/PNECs of norethisterone and ketoprofen decrease during the studied period. The long-acting calcium channel blocker (anti-hypertensive) amlodipine show an increased environmental risk with more than 800 % over the period due to increased sales.

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, segment 1;  
PEC/PNEC<0.3**

PEC/PNEC

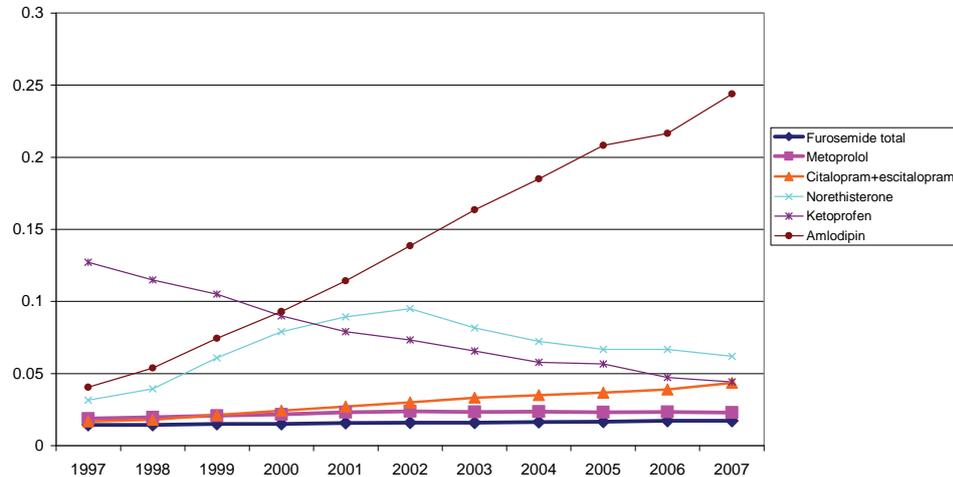


Figure 22. Data represents the environmental risks associated with drugs having low PEC/PNEC-ratios in Finland during 1997–2007.

None of the consumption patters displayed in Figure 22 would however merit for an environmental risk ( $PEC/PNEC > 1$ ). In Figure 23 however, some of the listed PEC/PNECs exceed unity (paracetamol and the drospirenone part of G03AA12 (also containing ethinyl estradiol)).

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, segment 2;  
PEC/PNEC<4**

PEC/PNEC

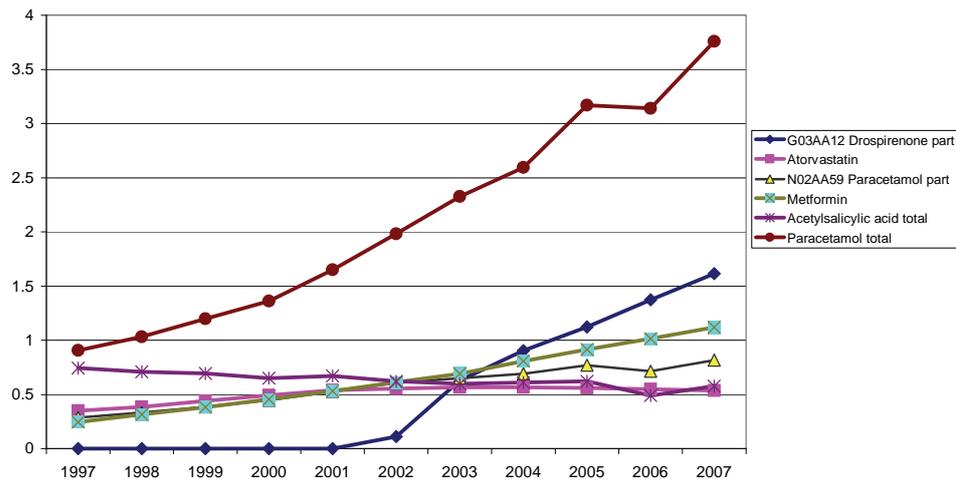


Figure 23. Data represents the environmental risks associated with drugs having intermediate PEC/PNEC-ratios in Finland during 1997–2007.

In Figure 24, pharmaceuticals associated with a high environmental risk are displayed. The only surprising result is the NSAID drug naproxen

associated with a virtually constant environmental risk between two and three, during the period. This is strikingly different from the other Nordic countries. The other substances associated with high environmental risk in Finland were estradiol (DDDs calculated in the same fashion as for estradiol formulations in Denmark, see section 3.2), ethinyl estradiol, estriol and ibuprofen.

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997–2007, segment 3;  $2 < \text{PEC/PNEC} < 25$**

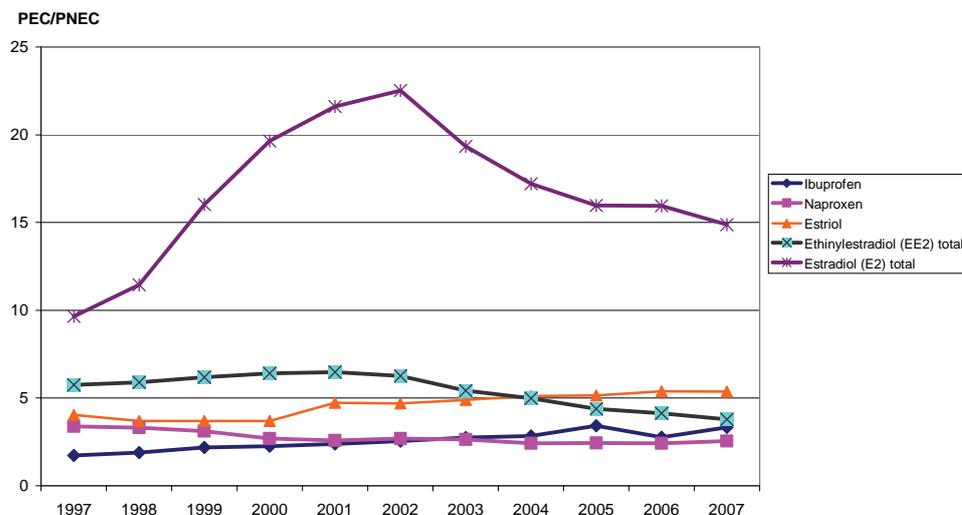


Figure 24. Data represents the environmental risks associated with drugs having high PEC/PNEC-ratios in Finland during 1997–2007.

### 3.6 Accumulated environmental risk in Finland 1997–2007

In terms of the accumulated environmental risk, also taking the persistence (assuming 0<sup>th</sup> order biodegradation kinetics) into consideration, four different segments could be identified (Figure 25). With respect to Figure 26, the drugs displayed there constitute high sales while having rather fast degradation kinetics; acetylsalicylic acid (being readily degraded in the environment), atrovastatin (being slowly degraded in the environment) and paracetamol (being inherently biodegradable). The accumulated PEC/PNEC never exceeds unity after a decade of constant supply. The pharmaceuticals included in this segment are furosemide (a loop diuretic used in the treatment of congestive heart failure and edema being potentially persistent), metoprolol (being potentially persistent), norethisterone (being potentially persistent), ketoprofen (being slowly degraded in the environment), amlodipine (being slowly degraded) and citalopram (summed with escitalopram, being potentially persistent). None of these substances possess very rapidly increasing sales (see Figure 22), but seem to have very slow biodegradation kinetics.

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, with respect to the reported biodegradation rates, segment 1;  $0.05 < PEC/PNEC < 0.5$**

PEC/PNEC

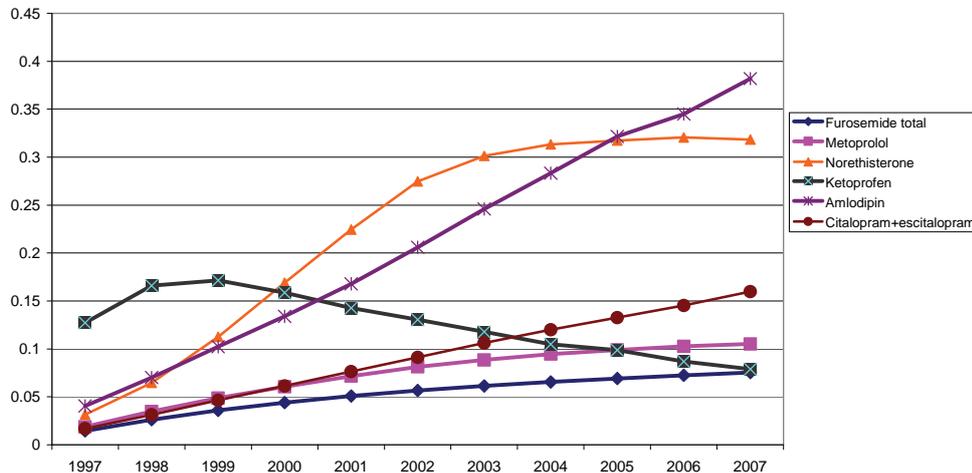


Figure 25. Data represents the accumulated environmental risks associated with drugs having medium PEC/PNEC-ratios in combination with medium-high persistence, in Finland during 1997–2007.

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, with respect to the reported biodegradation rates, segment 2;  $0.2 < PEC/PNEC < 1$**

PEC/PNEC

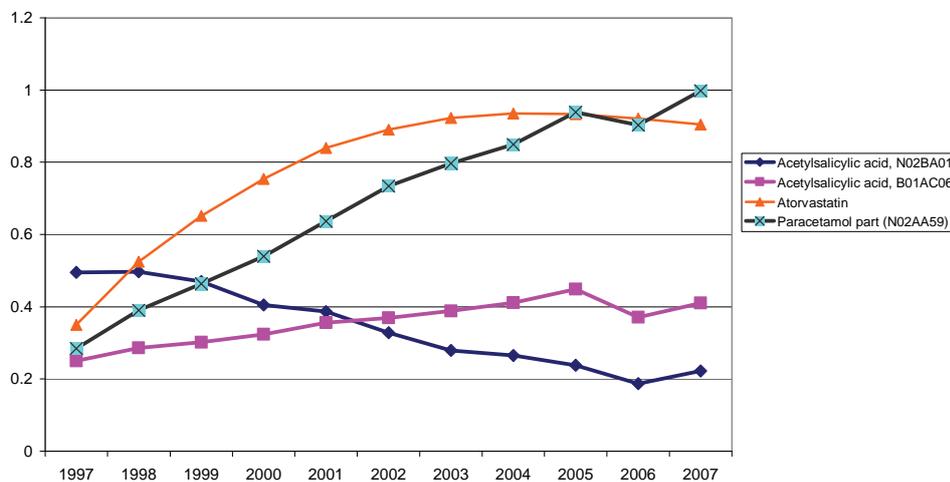


Figure 26. Data represents the accumulated environmental risks associated with drugs having medium PEC/PNEC-ratios in combination with low persistence, in Finland during 1997–2007.

In Figure 27, pharmaceuticals having high sales data in combination with medium to high persistence are displayed. The resulting accumulated environmental risk is in most cases exceeding unity after only a couple of years of constant supply to environment. Drospirenone (part of ATCG03AA12, assumed to be potentially persistent), metformin (being

potentially persistent), ibuprofen (being inherently biodegradable) and naproxen (being inherently biodegradable).

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, with respect to the reported biodegradation rates, segment 3;  $0.5 < PEC/PNEC < 5$**

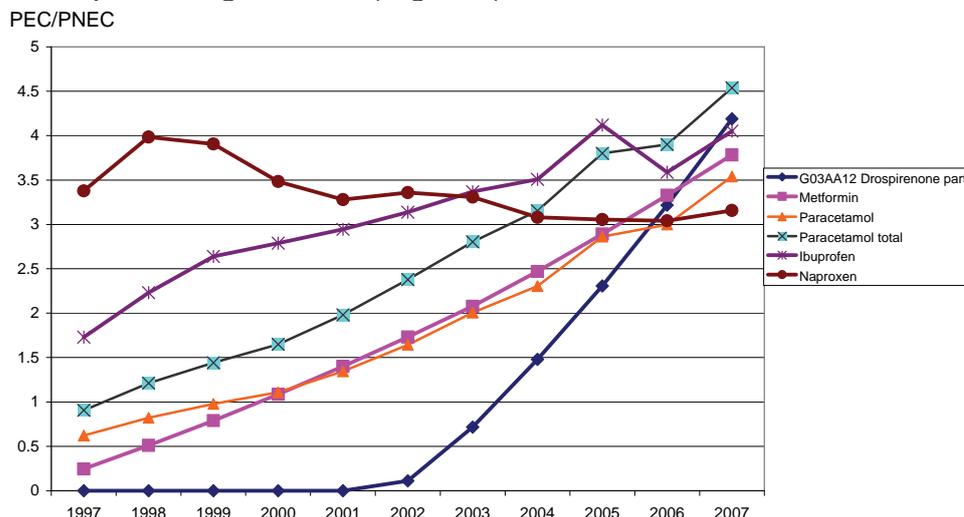


Figure 27. Data represents the accumulated environmental risks associated with drugs having high PEC/PNEC-ratios in combination with medium persistence, in Finland during 1997–2007.

In the last figure (Figure 28) displaying data from Finland, the substances normally associated with the highest environmental risk (the estrogens) are also the ones associated with the highest accumulated environmental risk; estradiol, ethinyl estradiol and estriol (all being classified as potentially persistent according to the fass.se website).

It is interesting to note that from the sales pattern for all these estrogenic substances the risk quotient reaches a plateau value around 2002 and no increase in the PEC/PNEC ratio seems likely even when accumulation is taken into consideration. Furthermore, the PEC/PNECs displayed as the maximum attainable values are indeed very high; 70 (estradiol), 20 (ethinyl estradiol) and 10 (estriol).

**Top of the PEC/PNEC-list for pharmaceuticals in Finland during 1997-2007, with respect to the reported biodegradation rates, segment 4;  $5 < \text{PEC/PNEC} < 80$**   
PEC/PNEC

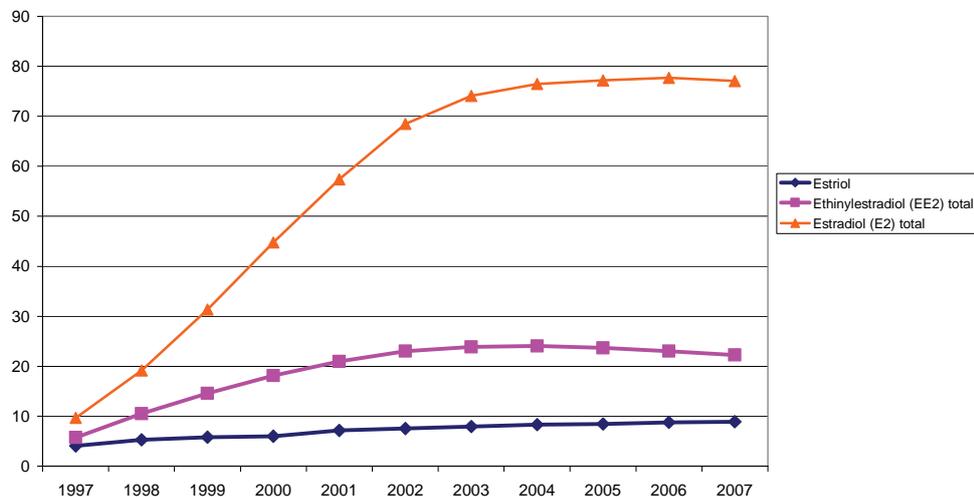


Figure 28. Data represents the accumulated environmental risks associated with drugs having medium PEC/PNEC-ratios in combination with low persistence, in Finland during 1997–2007.

### 3.7 Sales and consumption in Sweden 1997–2007

Data from Sweden contained total primary sales for the discrete years; 1997, 1999, 2001, 2003, 2005 and 2007. Treatment of sales data regarding hormones such as the ATC groups below, very much followed the DDD-assignment process performed for the Danish data set.

G03FA15, G03FA17, G03FB05, G03FB06, G03FB09, G03AC02, G03AC03, G03AC09, G03AB05, G03AB04, G03AA13, G03AA12, G03AA11, G03AA05, G03AA03, G02BB01, G03AA07, G03AA09, G03AB03

Nominally, the calculated DDDs were based on the UD (= active ingredient per unit dose), as specified in the guidance to Swedish doctors. For instance the ATC G02BB01 refers to a vaginal ring formulation containing both the estrogen ethinyl estradiol as well as the anti-estrogen etonogestrel. The flux of pharmaceuticals from the ring to the user is estimated to be 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol. Furthermore, the ring is supposed to be used during three consecutive weeks, followed by a one week of non-use. Thus the calculated “DDD” based on the UD-concept would then be 11.25 µg of ethinyl estradiol and 90 µg of etonogestrel. Even though it is likely that more than 50 % of the total estrogenic contents is remaining in the vaginal ring after use, that amount is not included in the PEC-calculation. In Figure 29–Figure 33 the annual sales of the top 33 formulations on the Swedish market 1997–2007 are displayed.

**Top-selling pharmaceuticals in Sweden during 1997-2007,  
segment 1; PEC<0.1 µg/l**

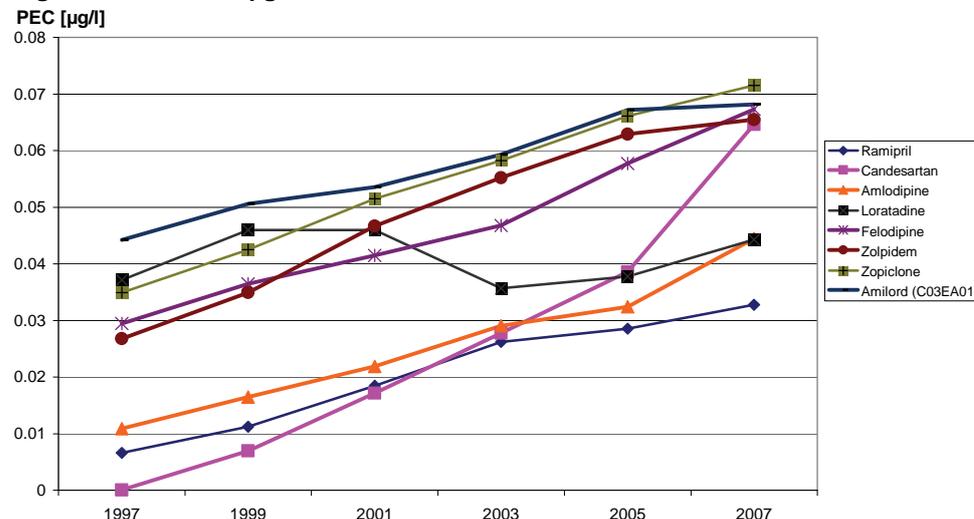


Figure 29. Data represents the PEC values of drugs sold in Sweden having median-PECs below 0.1 µg/l during 1997–2007.

In Figure 29 the pharmaceuticals having the lowest PECs are displayed. All drugs in this segment (except for loratidine) seem to increase in sales fairly uniformly during the period (by 70–400%). The PECs displayed would be very difficult to corroborate by measurements since the predicted concentrations are probably close to method LODs. Ramipril, an angiotensin-converting enzyme (ACE) inhibitor used to treat hypertension and congestive heart failure, exhibits a typical 400 % sales increase over the period. Belonging to a similar group of drugs is candesartan, being an angiotensin II receptor antagonist used mainly for the treatment of hypertension. Candesartan as market introduced in Sweden after 1997 and the increase in sales during the period corresponds to over 800 %. Loratidine is a drug used to treat allergies, and it is marketed for its non-sedating properties. In Sweden the sales of loratidine seems to be constant over the period. Finally, amiloride is a potassium-sparing diuretic used in the management of hypertension and congestive heart failure. Sales of amiloride in Sweden increased some 60 % over the period

**Top-selling pharmaceuticals in Sweden during 1997-2007,  
segment 2; PEC < 1 µg/l**

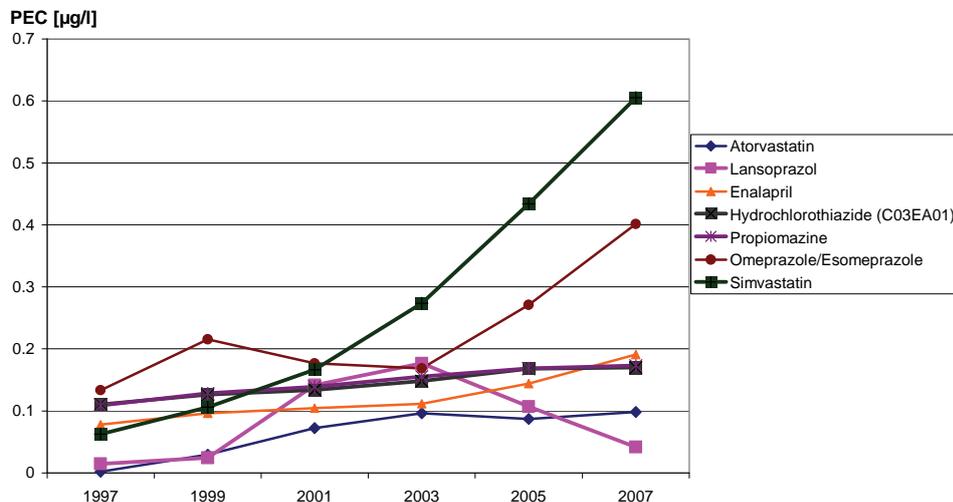


Figure 30. Data represents the PEC values of drugs sold in Sweden having median-PECs below 1 µg/l during 1997–2007.

In Figure 30, the next segment of pharmaceuticals is displayed. The median-PECs of these substances are high enough to enable confirmation by measurements in surface water. The sale of lansoprazole (proton pump inhibitor) is decreasing while the sales of omeprazole/esopromazole (also proton pump inhibitors) are increasing. Enalapril is an angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension. The sales of enalapril in Sweden were increased by 140 % during the period. Hydrochlorothiazide is diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood, and thus the cardiac output. It is sold in a vast number of formulations and combinations such as C09BA02, C09BA03, C09BA05, C09BA06, C09BA08, C09BA15, C09DA01, C09DA06, C03EA01 etc. Since hydrochlorothiazide-based diuretics do not have any DDDs it is very difficult to assess the summed PEC. Furthermore, if assuming a uniform DDD of 10 mg (most formulations are prescribed as one tablet, of 10–20 mg, per day), the ATC C03EA01 constitute 80 % of the total sales in the beginning of the period. In 2007 however, using the same calculation, the total consumption of hydrochlorothiazide may have doubled (summing all other ATC-groups containing hydrochlorothiazide). Thus, the final PEC of 2007 for hydrochlorothiazide might be as high as 0.34 µg/l. Atorvastatin and simvastatin are statins; used to control hypercholesterolemia (elevated cholesterol levels) and to prevent cardiovascular disease. Even though sales of simvastatin increased by almost 900 % over ten years, and the 2007 PEC was above 0.6 µg/l, it is highly unlikely that simvastatin would pose any environmental risk, nor be detected in any monitoring program, since it is a prodrug rapidly being converted upon digestion.

**Top-selling pharmaceuticals in Sweden during 1997-2007,  
segment 3; PEC<2 µg/l**

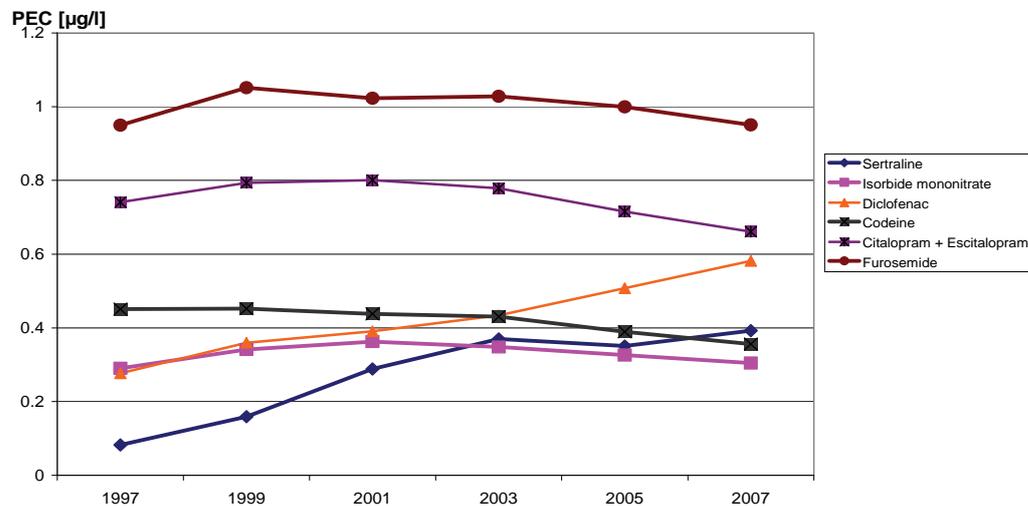


Figure 31. Data represents the PEC values of drugs sold in Sweden having median-PECs below 2 µg/l during 1997–2007.

In Figure 31 seven pharmaceuticals, sold in Sweden in amounts resulting in median-PECs just below 1–2 µg/l, are displayed. None of the pharmaceuticals in this segment show any dramatic increase in sales during the period (with the exception of the SSRI-drug sertraline, the average increase over the period 1997–2007 is < 50%). All drugs in Figure 31 have been thoroughly described in previous sections.

In Figure 32, drugs having PECs well over 1–2 µg/l are displayed. Similarly with the consumption pattern in Finland (see Figure 20 and Figure 21) metoprolol, naproxen, metformin, ibuprofen and acetylsalicylic acid are sold in such quantities to merit for high PECs. The consumption of metformin and ibuprofen seems to be steadily increasing in Sweden. During 1997–2007 both these drugs showed a sales increase by 400 %.

**Top-selling pharmaceuticals in Sweden during 1997-2007, segment 4;  
PEC < 20 µg/l**

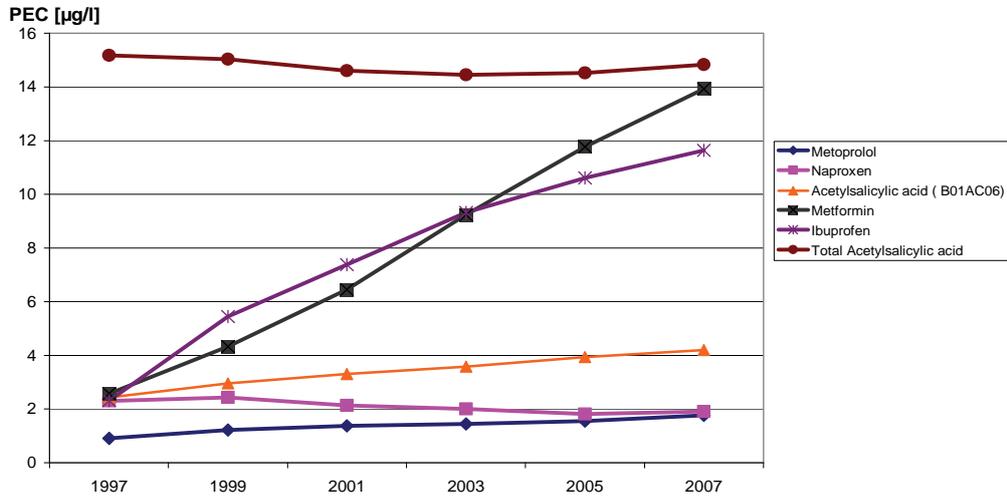


Figure 32. Data represents the PEC values of drugs sold in Sweden having median-PECs below 20 µg/l during 1997–2007.

Finally, in Figure 33, sales of the top selling pharmaceutical in Sweden, paracetamol, is displayed for the period. Sales of paracetamol increased by 50 % over the period studied, and the corresponding PEC is above 60 µg/l.

**Top-selling pharmaceuticals in Sweden during 1997-2007, segment 5; PEC > 50 µg/l (Paracetamol)**

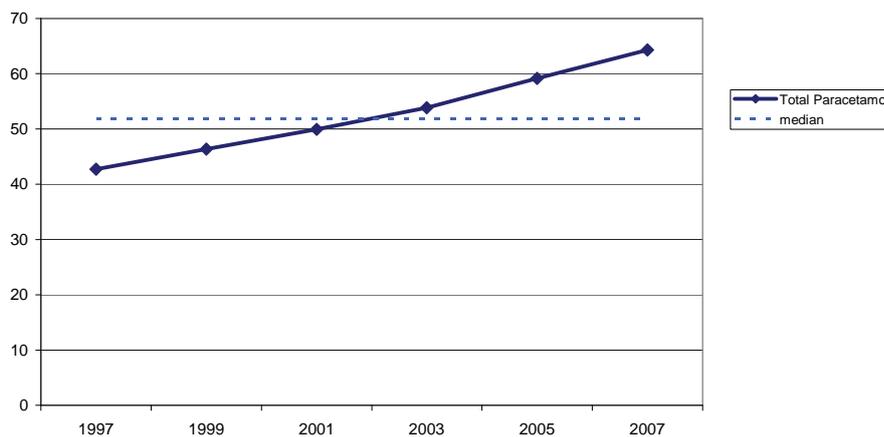


Figure 33. Data represents the PEC values of drugs sold in Sweden having median-PECs below 70 µg/l during 1997–2007.

### 3.8 Environmental risks in Sweden 1997–2007

When calculating environmental risks associated with the displayed levels of consumption of pharmaceuticals in Sweden 1997–2007, it was further corroborated that Sweden is similar to Finland, and to some extent, also Denmark.

In Figure 33, the lowest PEC/PNEC-quotients are displayed. The environmental risk is in all cases in Figure 34 below unity while with the fass.se-nomenclature amlodipine (a long-acting calcium channel blocker used as an anti-hypertensive and in the treatment of angina) and zolpidem (primarily used for the short-term treatment of insomnia) may be classified as having a “low environmental risk” (PEC/PNEC > 0.1 from 2003 and onwards). Simvastatin (orange line in Figure 34) could probably be omitted from further risk assessment due to its pro-drug character.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, segment 1; PEC/PNEC < 0.2**

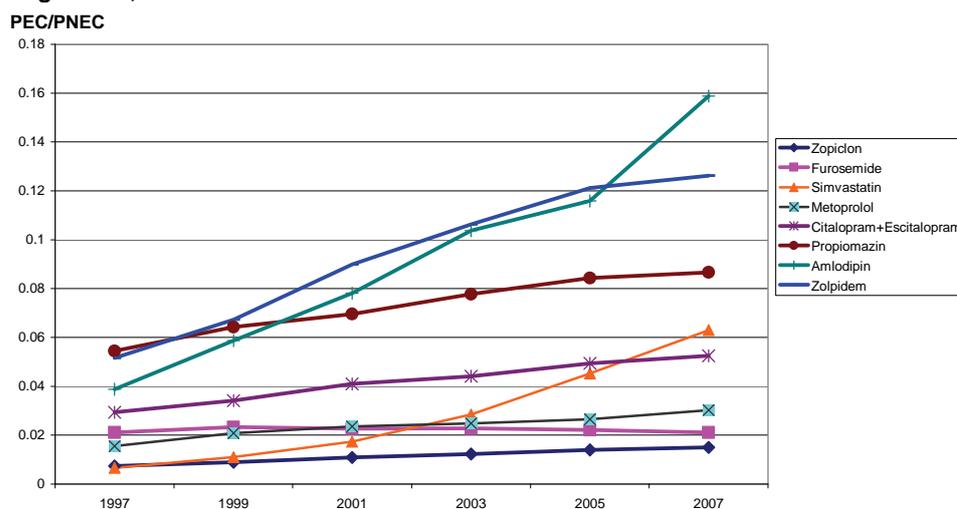


Figure 34. Data represents the environmental risks associated with drugs having low PEC/PNEC-ratios in Sweden during 1997–2007.

In Figure 35 several pharmaceuticals having 'Swedish' PEC/PNECs near one are displayed. For felodipin (a calcium channel blocker drug used to control hypertension), metformin (the oral biguanide-based anti-diabetic drug) and atorvastatin (the HMG-CoA reductase-inhibitor lowering the blood cholesterol level) there is a rapid, consecutive increase in the environmental risk due to increased consumption. The environmental risks associated with metformin and felodipine increased by 130 and 440 % respectively. It is interesting to note that the increased frequency of diseases of affluence such as some forms of diabetes and hypertension (thought to be a result of increasing wealth in a society, in contrast to diseases of poverty) in Sweden is fairly well resolved also in the calculated environmental risk.

The environmental risk associated with the use of the progestagen (anti-estrogen) Norethindrone is based on an assumed toxicity of 0.01 µg/l. This is an arguable assumption indeed. However, utilizing QSAR-models for endocrine disrupting substances have proven to be erroneous. Norethindrone is nearly quantitatively metabolized in the human body to tetrahydro-norethindrone, which has a lower but still comparable estrogenicity to estradiol. Therefore the assumption of a similar or an equipotent toxicity of norethindrone (compared with estradiol) may be valid.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, segment 1; PEC/PNEC<2**

PEC/PNEC

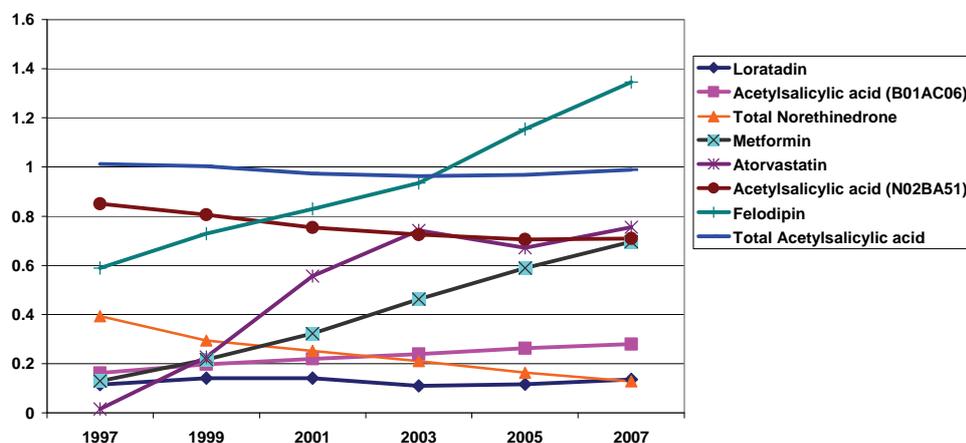


Figure 35. Data represents the environmental risks associated with drugs having intermediate PEC/PNEC-ratios in Sweden during 1997–2007.

In Figure 36 pharmaceuticals having intermediate-high environmental risk (the fass.se-scale) are displayed. It should be noted that for the NSAID drug diclofenac the standard NOEC of 10.000 µg/l for algae has not been used even though this is the toxicological endpoint being referred to in the fass.se-database. Instead a NOEC of 0.1 µg/l have been used in this assessment (for all Nordic countries), based on a chronic study on fish by Schwaiger et al., 2004.

From Figure 36 it is apparent that in Sweden the consumption of the SSRI-pharmaceutical sertraline renders that substance a position on the high environmental risk-segment.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, segment 3; PEC/PNEC<10**

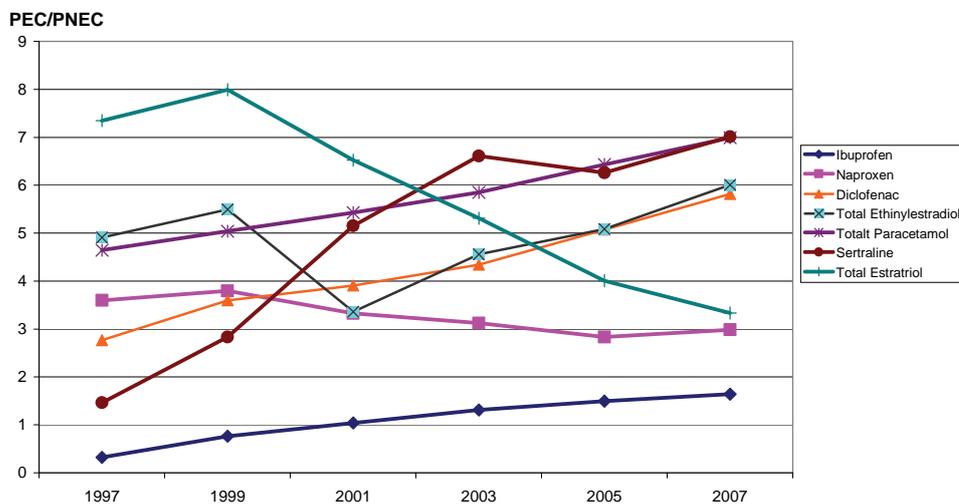


Figure 36. Data represents the environmental risks associated with drugs having high PEC/PNEC-ratios in Sweden during 1997-2007.

In the last figure discerning environmental risk in Sweden (Figure 37) the PEC/NEC of estradiol is plotted together with the corresponding environmental risk for the summed consumption of all estrogens in Sweden (estradiol, ethinyl estradiol and estriol).

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, segment 4; PEC/PNEC>10**

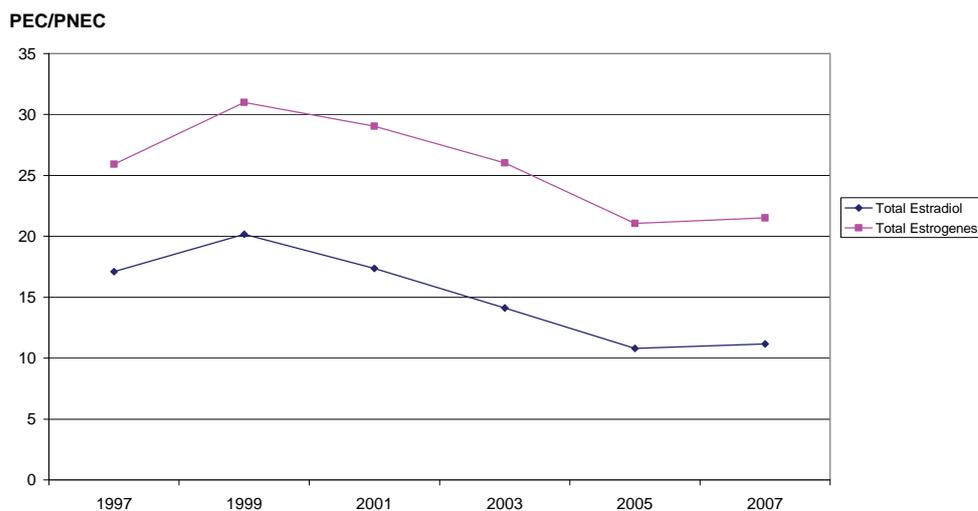


Figure 37. Data represents the environmental risks associated with estradiol having a very high PEC/PNEC-ratio, in Sweden during 1997-2007.

### 3.9 Accumulated environmental risk in Sweden 1997–2007

When taking also stipulated biodegradation rates into consideration it becomes evident that for a subset of the top-40 pharmaceuticals, accumulation in receiving waters may occur. Thus, the concentration build-up in some recipients is probably exceeding the effect concentrations in Figure 38 pharmaceuticals with the combination low PEC/PNECs and low persistence are displayed; simvastatin being readily biodegradable, amlodipine and zolpidem being slowly degraded and zopiclone, furosemide and citalopram/escitalopram (being potentially persistent).

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, with respect to the reported biodegradation rates, segment 1; PEC/PNEC<0.3**

PEC/PNEC

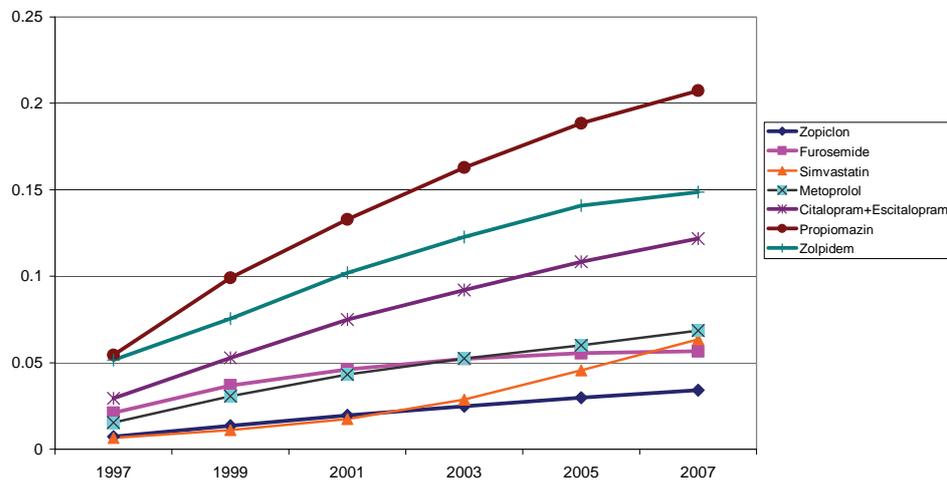


Figure 38. Data represents the accumulated environmental risks associated with drugs having low PEC/PNEC-ratios in combination with low persistence, in Sweden during 1997–2007.

In Figure 39 pharmaceuticals having medium to high PEC/PNECs are displayed. Norethinedrone and metformin being potentially persistent, felodipine being slowly degraded, and loratidine and acetylsalicylic acid being readily biodegradable.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, with respect to the reported biodegradation rates, segment 2; PEC/PNEC<2**  
PEC/PNEC

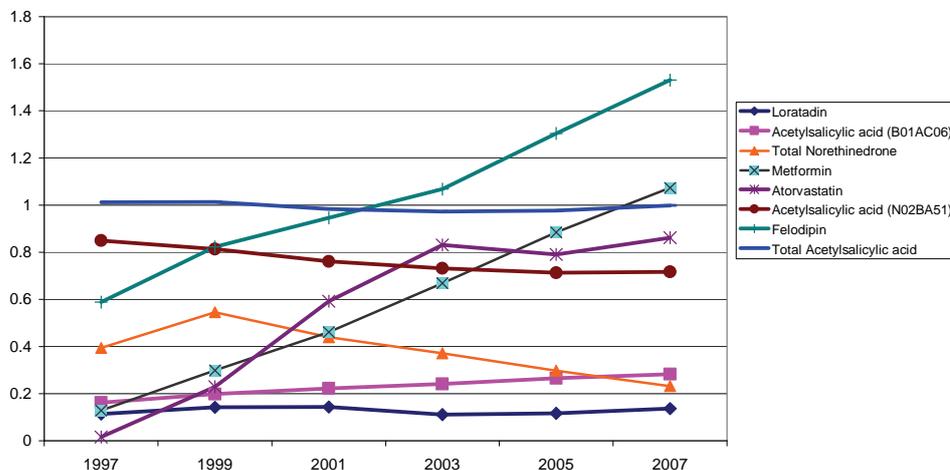


Figure 39. Data represents the accumulated environmental risks associated with drugs having medium PEC/PNEC-ratios in combination with low persistence, in Sweden during 1997–2007.

In Figure 40 pharmaceuticals having high PEC/PNECs and medium-to-high persistence are being displayed. The NSAID drugs (ibuprofen, naproxen and diclofenac) and paracetamol being inherently biodegradable while ethinyl estradiol, estriol and sertraline are potentially persistent.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, with respect to the reported biodegradation rates, segment 3; PEC/PNEC<15**  
PEC/PNEC

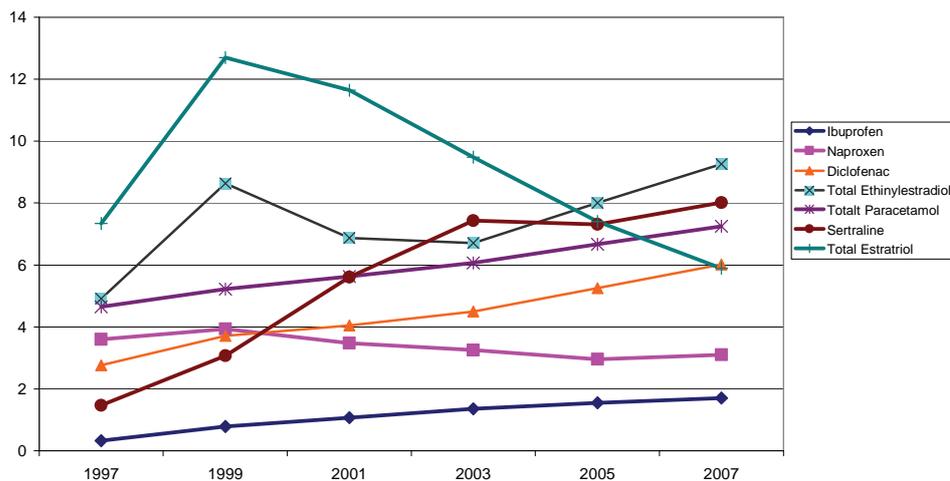


Figure 40. Data represents the accumulated environmental risks associated with drugs having intermediate-high PEC/PNEC-ratios in combination with high persistence, in Sweden during 1997–2007.

In Figure 41 the accumulated PEC/PNEC of estradiol is displayed, reaching a maximum value of 30 around 1999–2001 before showing a decreasing sales, and thus environmental risk.

**Top of the PEC/PNEC-list for pharmaceuticals in Sweden during 1997-2007, with respect to the reported biodegradation rates, segment 3; PEC/PNEC<15**

PEC/PNEC

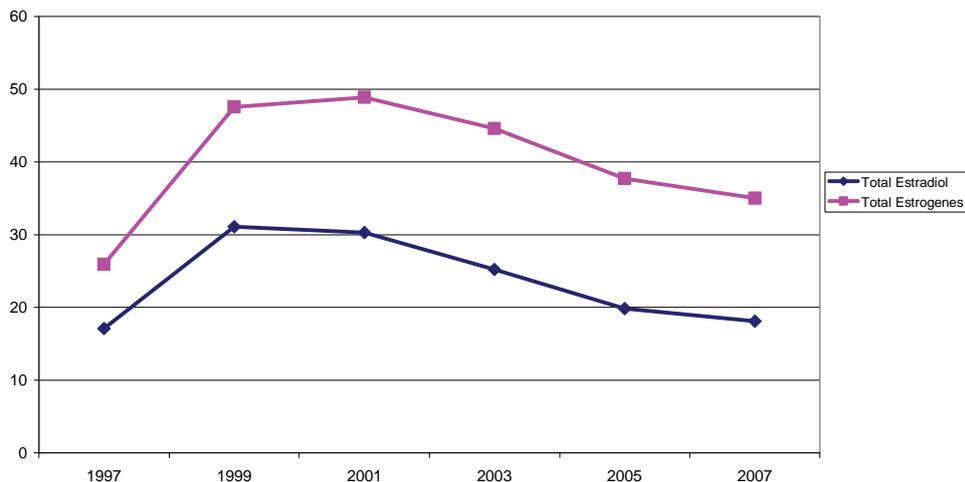


Figure 41. Data represents the accumulated environmental risks associated with estradiol having a high PEC/PNEC-ratio in combination with high persistence, in Sweden during 1997–2007.

### 3.10 Sales and consumption in Norway 1997–2007

The Norwegian dataset initially contained some gaps and some years were missing altogether (the years 1998, 2000 and 2001). The situation was partly improved by the addition of an independently retrieved sales data set regarding ATC-groups D, N, L, G and M, from Nasjonalt folkehelseinstitutt (Norwegian Institute of Public Health, courtesy of Solveig Sakshaug). In order to still be able to construct the plots necessary for comparison with the other Nordic countries, linear interpolation have occasionally been used. In some unfortunate cases a pharmaceutical is being introduced on the Norwegian market during the year 2000, and two year after the market introduction (2002), sales have increased dramatically due to full penetration of the market. In the data presented herein this renders the PEC-curve of such substances to become very steep (since interpolation from zero is performed, see celecoxib in Figure 42).

Since the Norwegian sales data set is a “composite” of several rounds of investigation and several independent inquiries, caution should be used when interpreting the Norwegian results.

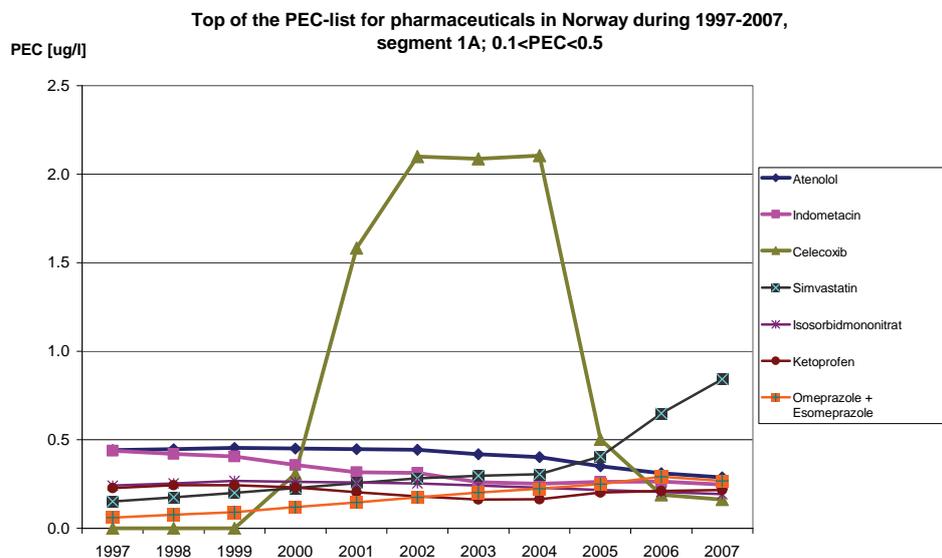


Figure 42. Data represents the PEC values of drugs sold in Norway having median-PECs below 0.5 µg/l during 1997–2007.

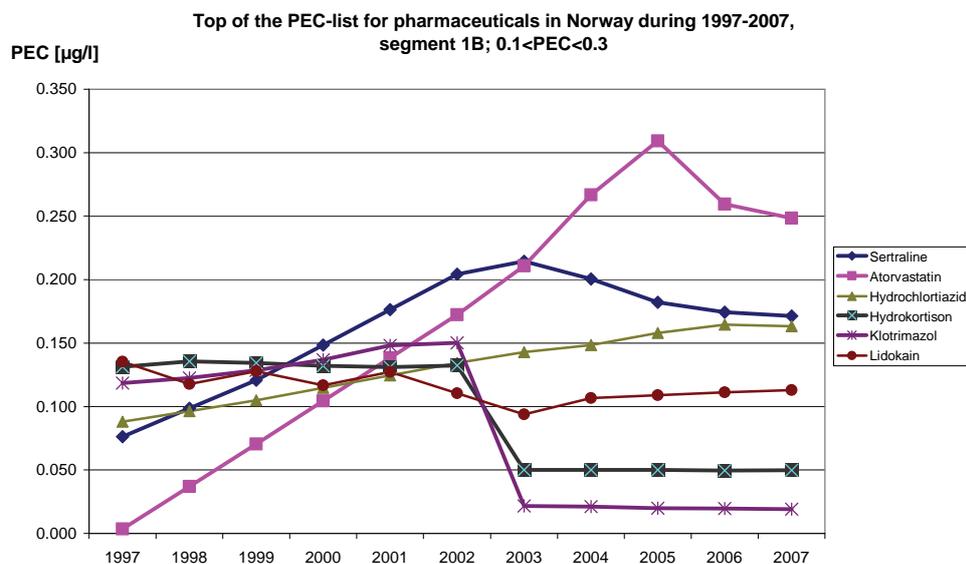


Figure 43. Data represents the PEC values of drugs sold in Norway having median-PECs below 0.3 µg/l during 1997–2007.

In Figure 42 and Figure 43 the pharmaceuticals having the low PECs are plotted (two figures to enhance the resolution). Pharmaceuticals having lower PECs (and hence lower sales) are not likely to be frequently detected in the Norwegian environment. Among the pharmaceuticals in these two plots several of them have already been briefly described in the sales analysis of the other Nordic countries (like atenolol, simivastatin, isorbidmononitrate, ketoprofen, omeprazole, sertraline and atorvastatin). However, the non-steroidal anti-inflammatory drug indometacin (com-

monly used to reduce fever, pain, stiffness, and swelling by inhibiting the production of prostaglandins) have not emerged as a drug having a PEC in the sub- $\mu\text{g}$  range in any of the other Nordic countries. Data on the NSAID-drug celecoxib is somewhat confusing but that stems from the fact that market introduction in Norway was probably in 2000–2001, and hence interpolation becomes difficult. Regardless of that, it is significantly different from the situation in the other Nordic countries, for instance Sweden where the maximum PEC of celecoxib was  $0.08 \mu\text{g}/\text{l}$  (corresponding to 500 kg).

The diuretic drug hydrochlorothiazide (a diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water) is on the Norwegian PEC-list but it has also emerged as a top-selling drug in Finland (Figure 19) and in Sweden (Figure 30). Clotrimazole (Klotrimazol in the Figure 43) is an antifungal medication commonly used in the treatment of fungal infections of both humans and animals such as vaginal yeast infections. Since this is a typical over-the-counter substance sold in various dosage forms, such as a cream, and also (especially in the case of ear infection as a combination medicine) the calculated sold amount should be interpreted with some care. Also in the Norwegian PEC-list is lidocaine, a common local anaesthetic and antiarrhythmic drug. Lidocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anaesthetic, and in minor surgery.

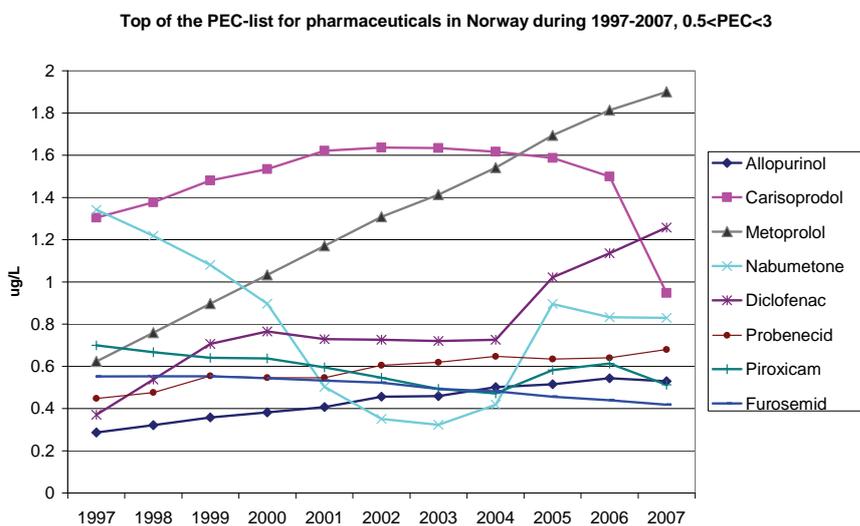
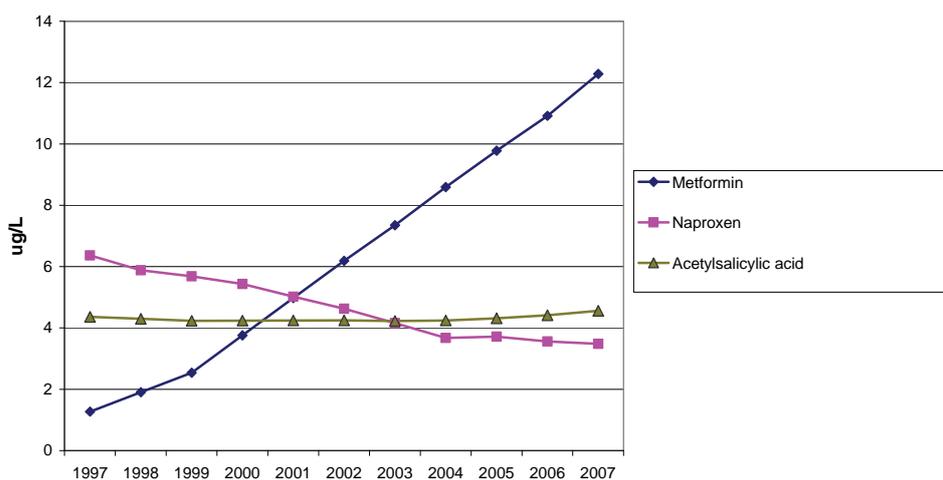


Figure 44. Data represents the PEC values of drugs sold in Norway having median-PECs below  $3 \mu\text{g}/\text{l}$  during 1997–2007.

In Figure 44 the next PEC-segment in Norway is displayed. Several drugs appear on this plot that seems unique for Norway like the centrally-acting skeletal muscle relaxant carisoprodol was withdrawn from the Norwegian market in 2008 (beyond the time interval of this particular study) and hence, this substance will probably not be an environmental issue. Al-

lopurinol, a drug used primarily to treat hyperuricemia (excess uric acid in blood plasma) and its complications, has steadily increasing sales in Norway (sales increased by > 45 % over the time period). Furthermore, nabumetone is a non-steroidal anti-inflammatory drug of the arylalkanoic acid family (which also includes diclofenac). This pharmaceutical has not emerged on any other Nordic PEC-list. Similar to nabumetone is piroxicam, a non-steroidal anti-inflammatory drug used to relieve the symptoms of rheumatoid and osteoarthritis, primary dysmenorrhoea, postoperative pain appears on the PEC-list. Also from Figure 44 and unique to Norwegian consumption is probenecid which is a uricosuric drug that increases uric acid excretion in the urine. It is primarily used in treating gout and hyperuricemia.

**Top of the PEC-list for pharmaceuticals in Norway during 1997-2007,  
3<PEC<10**



*Figure 45. Data represents the PEC values of drugs sold in Norway having median-PECs below 10  $\mu\text{g/l}$  during 1997–2007.*

From Figure 45, displaying pharmaceuticals having high PECs in Norway, it is evident that metformin, the oral anti-diabetic drug from the biguanide class (the first-line drug for the treatment of type 2 diabetes) has a corresponding sales increase of 85 % in a decade in Norway, which seems to be in agreement with the overall Nordic situation. The Nordic PECs of metformin were between 10  $\mu\text{g/l}$  (Denmark 2007, Figure 5) and 22  $\mu\text{g/l}$  (Finland, 2007). Acetylsalicylic acid on the other hand seems to have a almost constant sales in Norway.

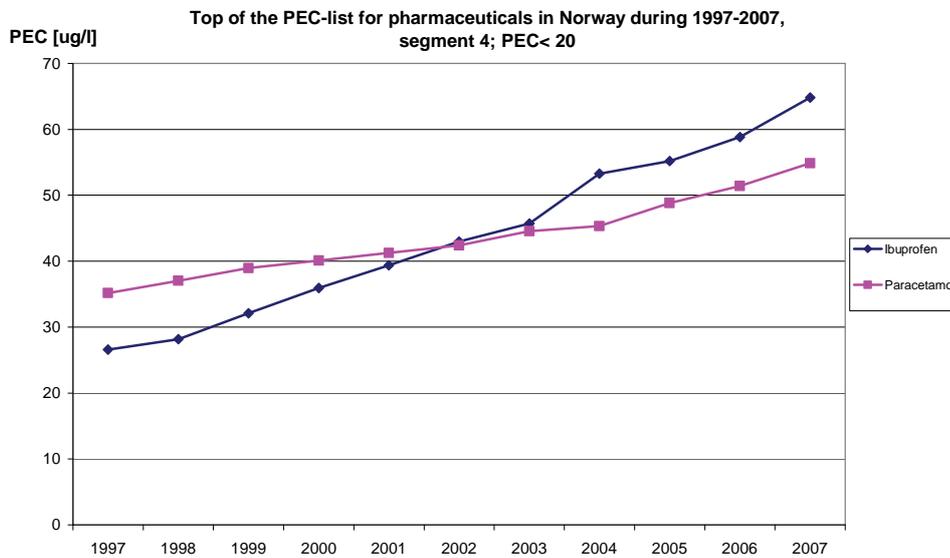


Figure 46. Data represents the PEC values of drugs sold in Norway having median-PECs below 70  $\mu\text{g/l}$  during 1997–2007.

In Figure 46, the top-fraction of the Norwegian sales list is displayed. As in the other Nordic countries ibuprofen and paracetamol corresponds to the drugs having PECs well over 50  $\mu\text{g/l}$ .

### 3.11 Environmental risks in Norway 1997–2007

In Figure 47-Figure 49 the apparent environmental risk for human pharmaceuticals sold in Norway 1997–2007 are displayed.

In Figure 47 the low risk pharmaceuticals are displayed. Sales of acetylsalicylic acid seems to be somewhat lower in Norway compared with the other Nordic countries

All pharmaceuticals present in Figure 48 depict the medium environmental risk segment, and are known to have similar PEC/PNEC-ratios in Sweden and Denmark. However, the rapid increase in the risk associated with the progestogen drospirenone that is experienced in the Norwegian data set may stem from an increased consumption of the contraceptive combination pill Yasmin® that was marketed in 2000, resulting in reduced consumption of other contraceptive combination pills.

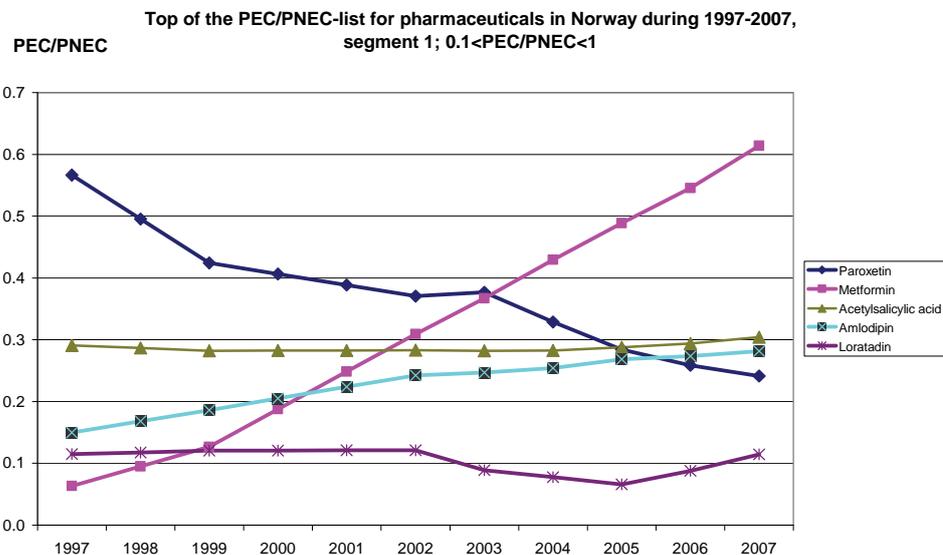


Figure 47. Data represents the environmental risks associated with drugs having low PEC/PNEC-ratios in Norway during 1997–2007.

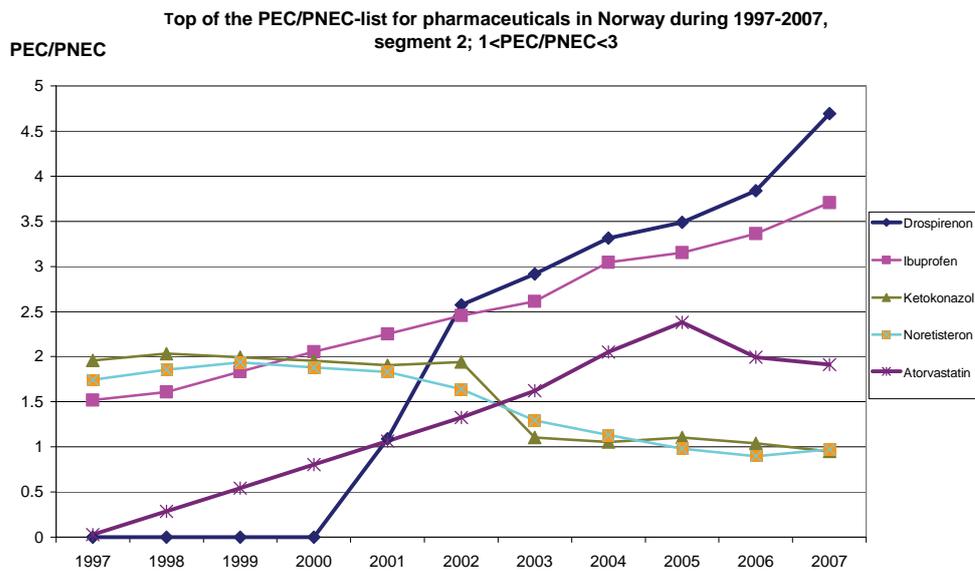


Figure 48. Data represents the environmental risks associated with drugs having low-medium PEC/PNEC-ratios in Norway during 1997–2007.

Top of the PEC/PNEC-list for pharmaceuticals in Norway during 1997-2007, 3<PEC/PNEC<10

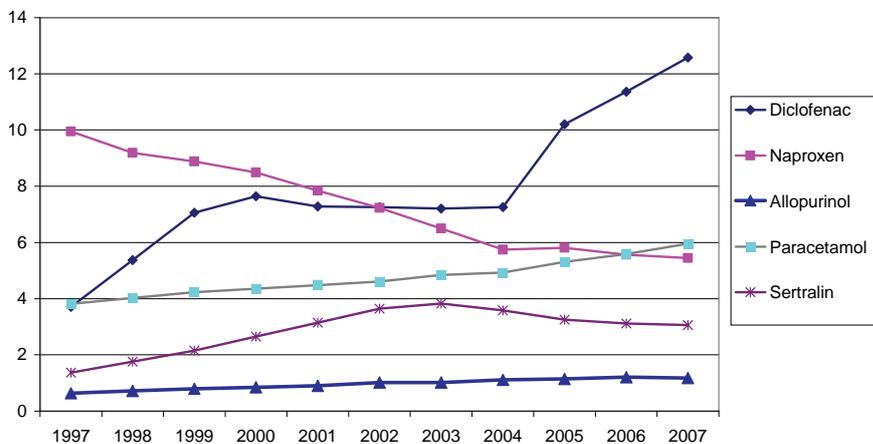


Figure 49. Data represents the environmental risks associated with drugs having high PEC/PNEC-ratios in Norway during 1997–2007.

In Figure 49, the intermediate-to-high PEC substances are displayed and the consumption data very much resembles the data from the other Nordic countries. The only major difference between Norway and the other Nordic countries is that ibuprofen is not the dominating NSAID drug; instead both naproxen and diclofenac are consumed in higher quantities. Like in the other Nordic countries sertraline and paracetamol place themselves in top.

Top of the PEC/PNEC-list for pharmaceuticals in Norway during 1997-2007, segment 4; PEC/PNEC>10

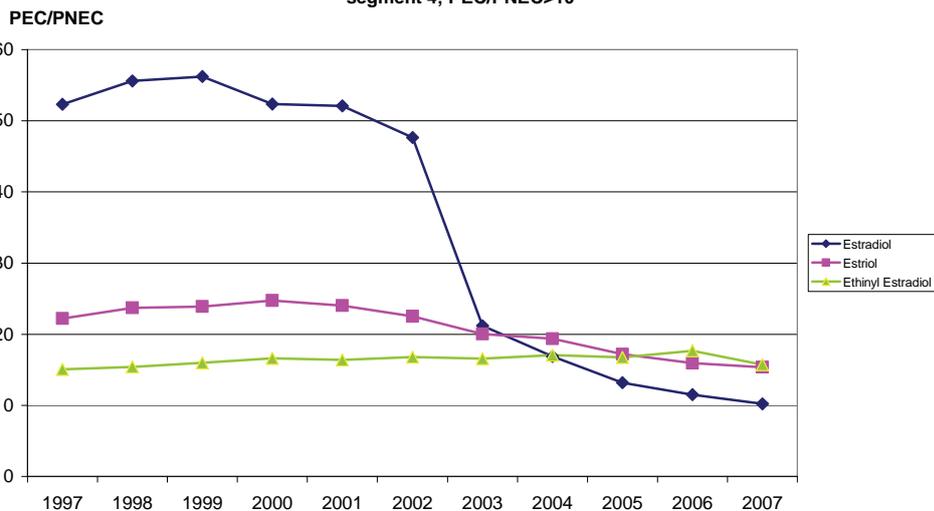


Figure 50. Data represents the environmental risks associated with drugs having very high PEC/PNEC-ratios in Norway during 1997–2007.

Finally, in Figure 50, the estrogens are displayed. As in the other Nordic countries, these substances pose the highest environmental risk. The decline in the sales of estradiol-based medicines for hormone replacement therapy and hypoestrogenism may, as also noticed also in the other Nordic countries, be attributed to an increasing awareness of the fact that consumption of estradiol increases the risk of several serious conditions such as coronary thrombosis (Miller et al., 2006), arterial thrombosis (Abu-Fanne et al., 2008) and breast cancer (Levenson et al., 1997, LI et al., 2006).

### 3.12 Accumulated environmental risk in Norway 1997–2007

In Figure 51 – Figure 53, the accumulated environmental risk associated with pharmaceuticals sold in Norway are displayed. Neither type of drugs present, nor the actual PEC/PNEC-values differs significantly from the situation in Sweden or Denmark.

Some remarks of drugs not present in the accumulated PEC/PNEC-plots from the other Nordic countries; Paroxetine (Figure 51) is a selective serotonin reuptake inhibitor (SSRI) antidepressant. Sales in the other Nordic countries do not merit this substance to enter any of the top charts with respect to environmental risk.

The pharmaceuticals appearing in Figure 52 – Figure 53, having a very high accumulated environmental risk in Norway, are very much the identical ones also appearing in the other Nordic countries.

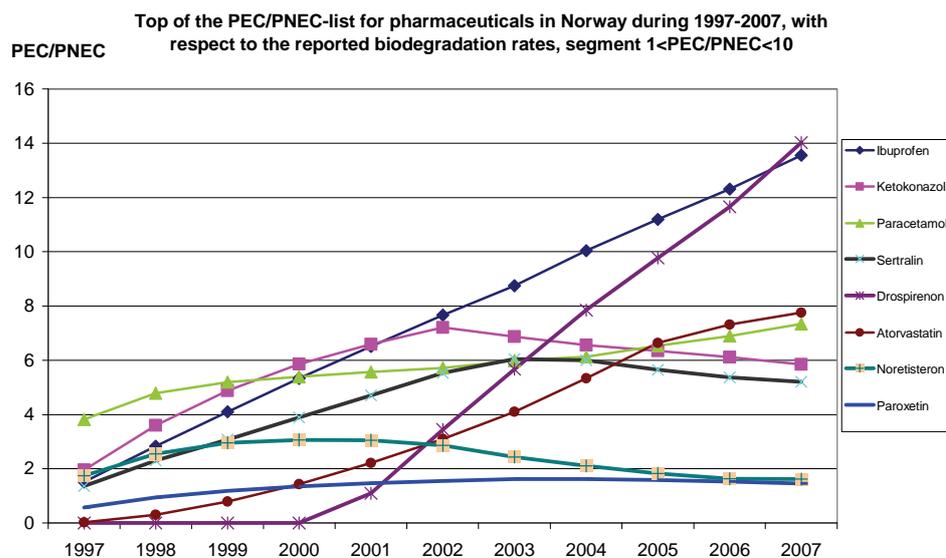


Figure 51. Data represents the accumulated environmental risks associated with drugs having low-intermediate PEC/PNEC-ratios in combination with intermediate persistence, in Norway during 1997–2007.

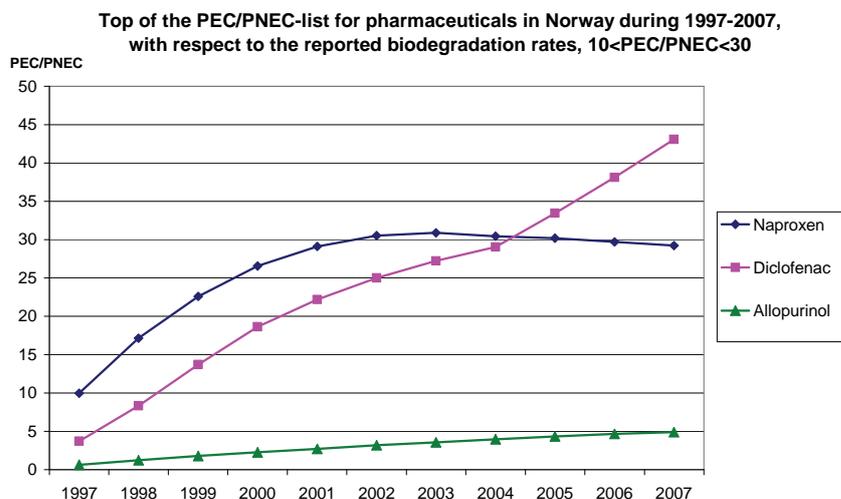


Figure 52. Data represents the accumulated environmental risks associated with drugs having high PEC/PNEC-ratios in combination with intermediate persistence, in Norway during 1997–2007.

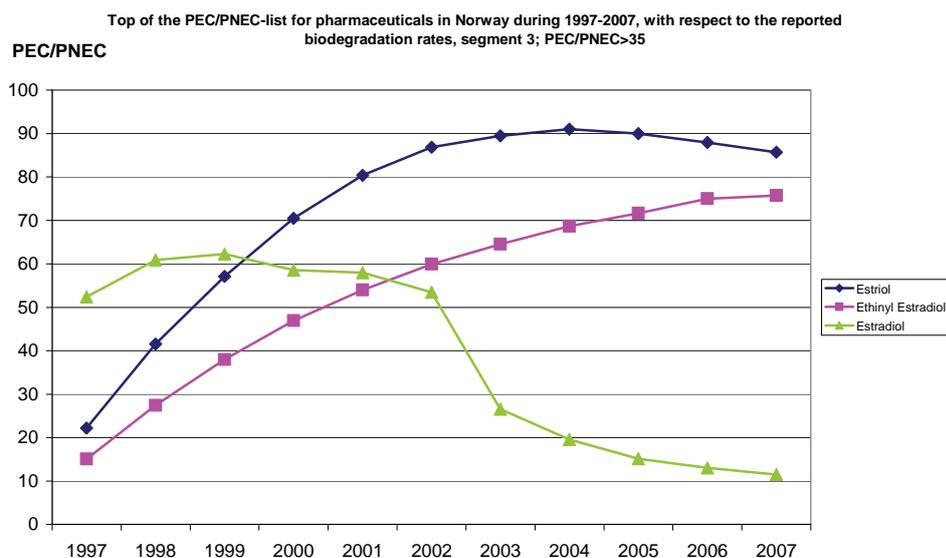


Figure 53. Data represents the accumulated environmental risks associated with drugs having high PEC/PNEC-ratios in combination with intermediate persistence, in Norway during 1997–2007.

### 3.13 Sales and Consumption on Iceland 1997–2007

Sales data of human pharmaceuticals from Iceland comprised very resolved data (down to the annual number of packages and patches sold of each brand or producer) and an algorithm was developed in Microsoft Excel VBA editor, to sum all drugs from identical ATC-codes. The number of sold packages was then converted into DDDs based on dose infor-

mation by the algorithm. The number of sold DDDs was then converted into kg and corresponding PEC-values also taking the population of Iceland into consideration (Figure 54).

Regarding the year 2007, sales data was also parameterized between primary and secondary sales. Since information on primary and secondary sales contributions respectively were only available for this year, no further analysis was made on the contribution from hospital pharmacies.

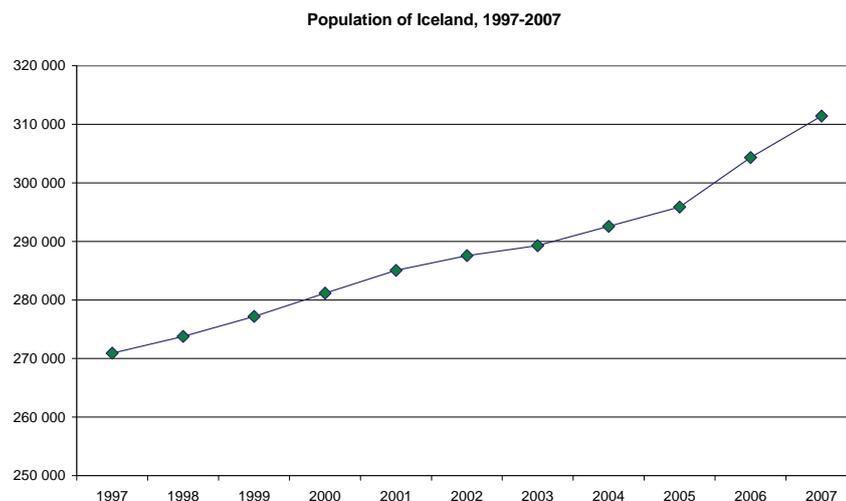


Figure 54. Population in Iceland 1997–2007. From 1997–2007 the population increased by 14 %.

Since Iceland is situated in the mid-Atlantic, the normal PEC-calculation, based on a dilution of the WWTPs effluent concentrations by a factor of ten seems a bit unrealistic. However, this is the standard method used and PEC-data may turn out to be useful also for Icelandic stakeholders since it will allow for an international comparison. Environmental impacts from effluent discharges could in theory arise only in the Reykjavik area (at the Faxe fjord), which is populated by ca 200 000 inhabitants. However, considering the geographical position in the Atlantic, the small population of Iceland and the fact that hot, geothermal water is often mixed with the WWTP influent water, renders it very unlikely that pharmaceuticals would build up in significant concentrations. Furthermore, the sea currents close to land on Iceland are very strong which suggests a very rapid mixing and dilution of effluent discharges (Several north Atlantic currents renders the water circumferencing Iceland to flow in a mainly clockwise direction around the island. The warm North Atlantic Drift Current gives rise to the Irminger Current south of Iceland. The Irminger current travels along the western and northwestern coasts until it meets the polar water of the East Greenland (Reynaud et al., 1995, Bersch M, 1995, Krauss W, 1995).

The top-selling drugs on Iceland are listed in three figures; Figure 55;  $0.1 < PEC < 0.3$ , Figure 56;  $0.3 < PEC < 1$ , and Figure 57;  $1 < PEC < 3$ .

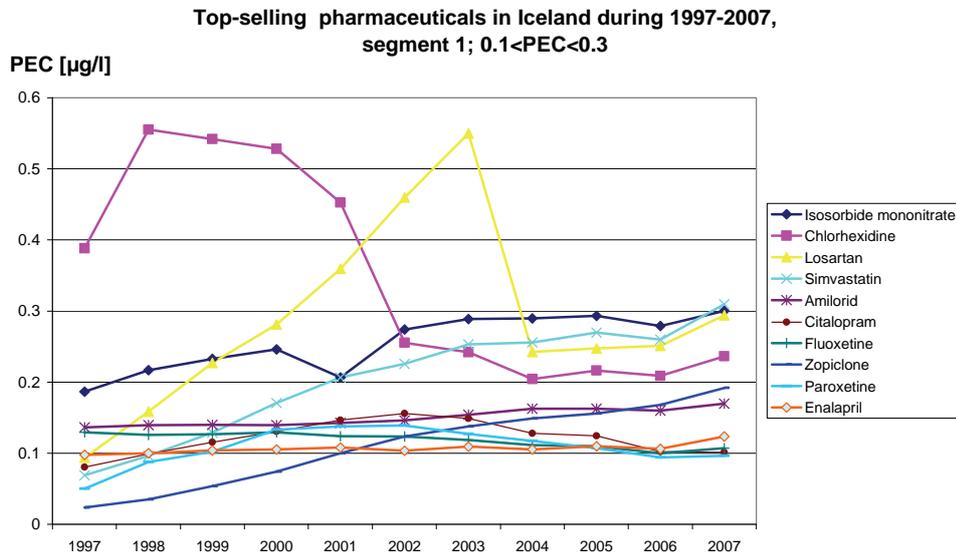


Figure 55. Data represents the PEC values of drugs sold on Iceland having median-PECs below  $0.3 \mu\text{g/l}$  during 1997–2007.

In Figure 55 the pharmaceuticals sold on Iceland having low PECs are listed. Losartan, the angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension) show a peak sales in 2003 and consumptions now seems to have stabilized. Chlorhexidine, a chemical antiseptic that is also bactericidal to both gram positive and gram negative microbes shows decreasing sales (after 1998). Fluoxetine (“Prozac”) the SSRI drug showed a steady decrease (-20 %) in sales during the period. Zopiclone and simivastatin showed increased sales of 87 and 77 %, respectively. All other pharmaceuticals seem to experience an increase in the sales between 19–48 %, probably reflecting the increasing population and/or the increased elderly population.

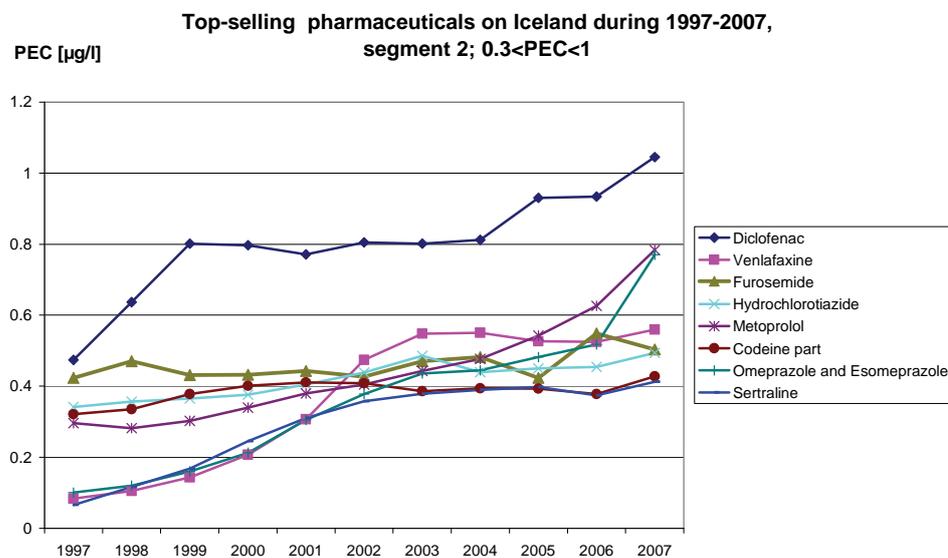


Figure 56. Data represents the PEC values of drugs sold on Iceland having median-PECs below  $1 \mu\text{g/l}$  during 1997–2007.

In Figure 56 the next segment of pharmaceuticals sold on Iceland are depicted. Apart from the antidepressant venlafaxine (an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class, first market introduced on the market in 1993) the other drugs appearing in the plot are all high-sales pharmaceuticals also in the other Nordic countries. Venlafaxin is prescribed for the treatment of major depression and anxiety disorders, among other uses. Like the situation in both Denmark and Sweden, furosemide showed only a small increase in sales over the period whereas the other drugs increased their sales by 54–86 %.



Figure 57. Data represents the PEC values of drugs sold on Iceland having median-PECs below  $3 \mu\text{g/l}$  during 1997–2007.

In Figure 57 pharmaceuticals with PECs well over unity are displayed. Interestingly there is no dramatic increase in sales during the period, in fact naproxen shows decreasing sales while the sales of the  $\beta$ 1-receptor selective antagonist atenolol (a drug belonging to the group of  $\beta$ -blockers, a class of drugs used primarily in cardiovascular diseases) increases by 24 %.

The last figure displaying PEC-values (Figure 58) the real top-sellers are depicted, and as in the case of all other Nordic countries acetylsalicylic acid, ibuprofen and paracetamol have high PEC-values. However, as shown in the risk (PEC/PNEC) assessment figures, both acetylsalicylic acid and paracetamol are prone to biodegradation.

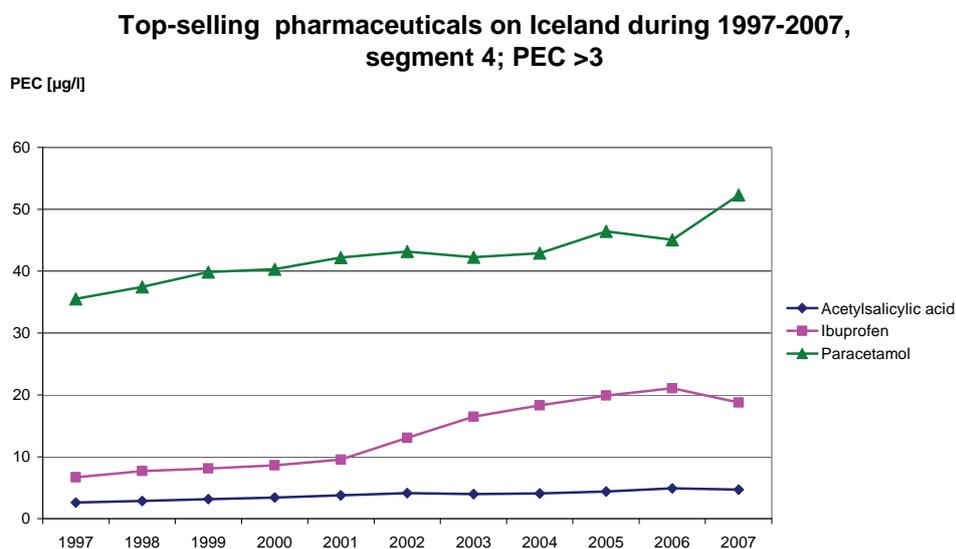


Figure 58. Data represents the PEC values of drugs sold on Iceland having median-PECs above 3  $\mu\text{g/l}$  during 1997–2007.

### 3.14 Environmental risk of pharmaceuticals on Iceland 1997–2007

Regarding the environmental risk assessment of pharmaceuticals sold on Iceland, the very same difficulties regarding drugs of ATC group G (genito urinary system and sex hormones) was encountered as in the other Nordic countries. For the ATC-groups below, the assignment of the DDD was performed using the Swedish definitions (the construction of the DDD from typical formulations on the Swedish market).

G03FA15, G03FA17, G03FB05, G03FB06, G03FB09, G03AC02, G03AC03, G03AC09, G03AB05, G03AB04, G03AA13, G03AA12, G03AA11, G03AA05, G03AA03, G02BB01, G03AA07, G03AA09, G03AB03

Among the low risk drugs sold on Iceland (see Figure 59) one finds a very familiar pattern of pharmaceuticals very similar to that seen in the other Nordic countries. With the exception of the statin drug atorvastatin (used for lowering blood cholesterol) the pharmaceuticals of this PEC/PNEC interval (0.1–1) display only subtle changes over time in the calculated environmental risk, i.e., sales seems fairly constant. Atorvastatin, on the other hand displays an increase in sales between 1998 and 2007 by 99 % (introduced on the market in 1998), and hence also in the apparent environmental risk.

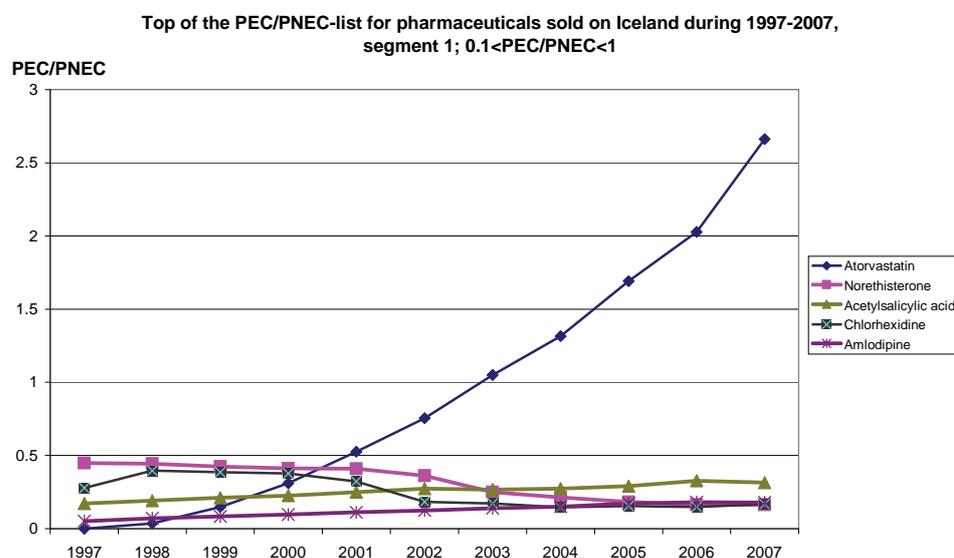


Figure 59. Data represents the environmental risks associated with drugs having low PEC/PNEC-ratios on Iceland during 1997–2007.

In Figure 60 data represents the environmental risks associated with drugs having median PEC/PNEC-ratios on Iceland during 1997–2007. The retrospective environmental risk concerning three pharmaceuticals in the medium-to high environmental risk is displayed. As can be observed in the plot, estriol and fluoxetine seems to be consumed in fairly constant amounts while the consumption of ibuprofen is increasing (during the period 1997–2007, consumption of ibuprofen on Iceland increased by 70 % and the current level of active ingredient sold is almost 4 tonnes in 2007).

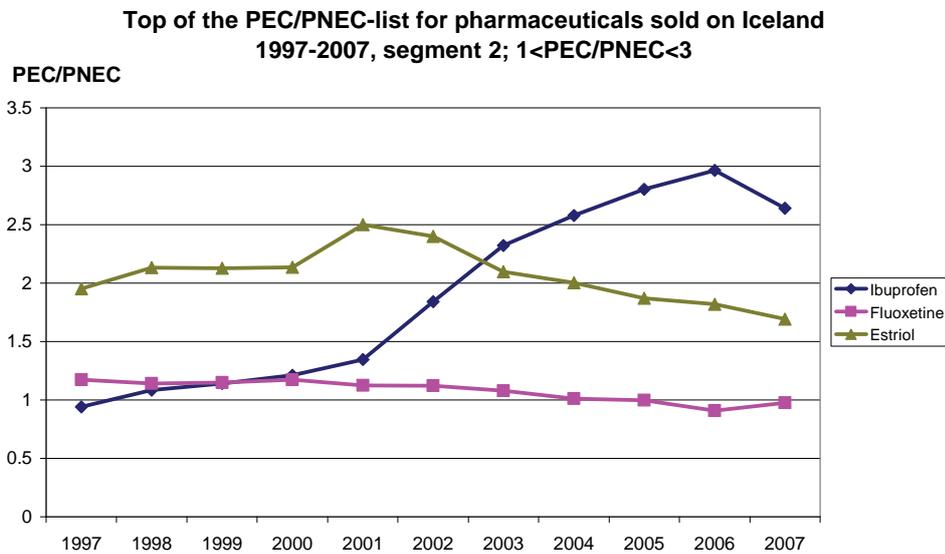


Figure 60. Data represents the environmental risks associated with drugs having median PEC/PNEC-ratios on Iceland during 1997–2000

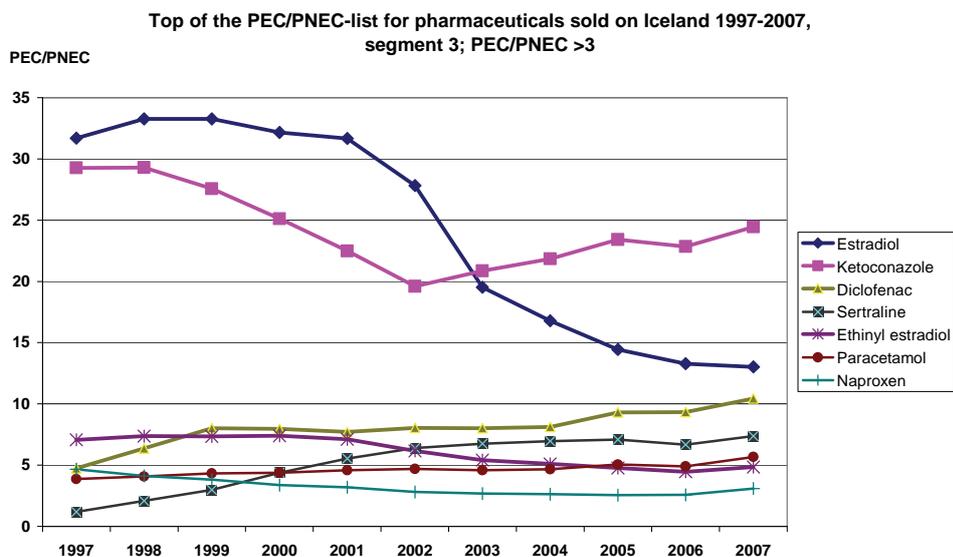


Figure 61. Data represents the environmental risks associated with drugs having low PEC/PNEC-ratios on Iceland during 1997–2007.

In Figure 61 the high risk pharmaceuticals sold on Iceland are displayed. As can be seen, a subset of these pharmaceuticals (diclofenac, naproxen, sertraline, ethinyl estradiol and paracetamol) has PEC/PNEC quotients below 10 and their corresponding consumption seems constant over time. The other subset of pharmaceuticals consist of the estrogen estradiol which has a very high PEC/PNEC quotient ( $>10$ ) and the apparent consumption seems to shift over time. In the case of estradiol, the decreased

sales have also been observed in the other Nordic countries and could, as stated before, perhaps be associated to the increased awareness of the risks associated with estradiol-based hormone replacement therapy (coronary thrombosis and breast cancer)

### 3.15 Accumulated environmental risk of pharmaceuticals on Iceland 1997–2007

When taking biodegradation rate and the potential to persist and accumulate in the environment into consideration it is obvious that the consumption of both atorvastatin and fluoxetine on Iceland may result in an environmental impact (Figure 62). Since both these drugs have been reported to be potentially persistent (i.e., the fraction of the sold amount still remaining in the environment after 12 months was assumed to be 80 %) there will be a build-up over time and the annual PEC/PNEC-contribution (PEC/PNEC = 2.75 as a maximum at 2007) will be increased by a factor of 2.5 in a ten-year perspective. Also norethisterone have been reported to be potentially persistent in the fass.se database. However, the overall consumption is decreasing between 1997–2007 and hence the potential build-up is counteracted by that.

The NSAIDs ibuprofen and naproxene have been reported to be relatively biodegradable (10 and 20 % of the sold amount still remaining in the environment after 12 months, respectively) and therefore concentration build-up is very slow despite the fact that consumption of the these substances is increasing on Iceland.

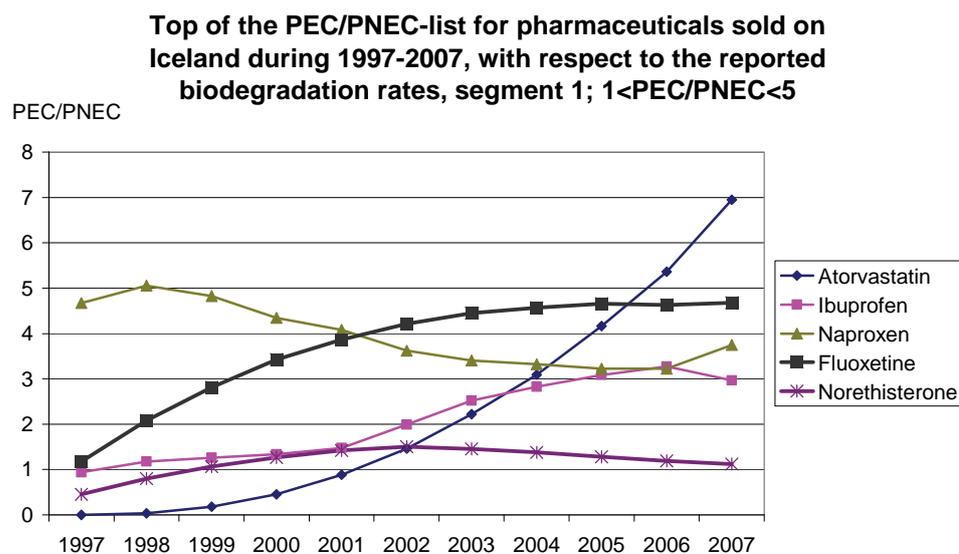


Figure 62. Data represents the accumulated environmental risks associated with drugs having intermediate-high PEC/PNEC-ratios in combination with intermediate-intermediate persistence, on Iceland during 1997–2007.

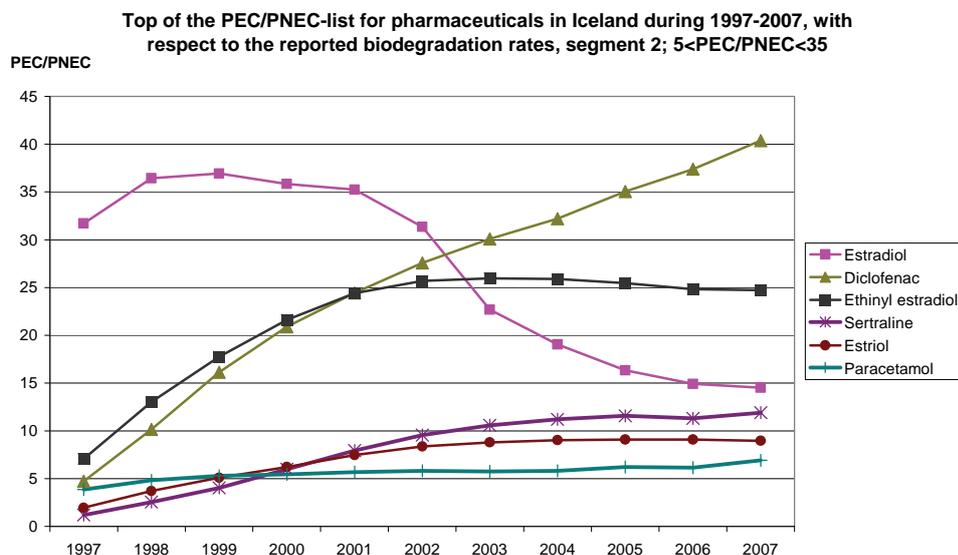


Figure 63. Data represents the accumulated environmental risks associated with drugs high PEC/PNEC-ratios in combination with intermediate-high persistence, on Iceland during 1997–2007.

In Figure 63 six pharmaceuticals having high accumulated PEC/PNEC quotients are displayed. Estriol, ethinyl estradiol and diclofenac are all classified as “potentially persistent” (and hence the fraction of the sold amount still remaining in the environment after 12 months was assumed to be 80 %). This explains the very rapid increase in apparent environmental risk with respect to diclofenac (rapidly increasing sales, 55 % in ten years in combination with low biodegradation rate). Ethinyl estradiol on the other hand experience a 46% drop in sales during the period while this will be partly counteracted by the low biodegradation rate (compare with Figure 61). The sales of Estradiol is decreasing and the substance is readily biodegradable according to the fass.se database. This renders the substance to have a rather fast declining environmental risk. Paracetamol (20 % of the sold amount still remaining in the environment after 12 months) and sertraline (40 % of the sold amount still remaining in the environment after 12 months) show an almost constant environmental risk accumulated over a decade.

## 4. Ketoconazole, an in-depth analysis

Ketoconazole (CAS 65277-42-1) has been given a special chapter in this report where consumption of the drug in the Nordic countries has been subjected to an in-depth analysis. Assumptions of the consumption, and thus the PEC of ketoconazole, are prone to be associated with a large uncertainty, due to the multitude of different preparations available.

Ketoconazole is a synthetic antifungal drug used to prevent and treat skin and fungal infections (*medline plus*), especially in immunocompromised patients such as those with AIDS (Oriba et al., 1990). Ketoconazole is sold commercially as an anti-dandruff shampoo, under several different brand names.

Ketoconazole is lipophilic,  $\log K_{ow} \sim 4.4$ , which leads to accumulation in fatty tissues.

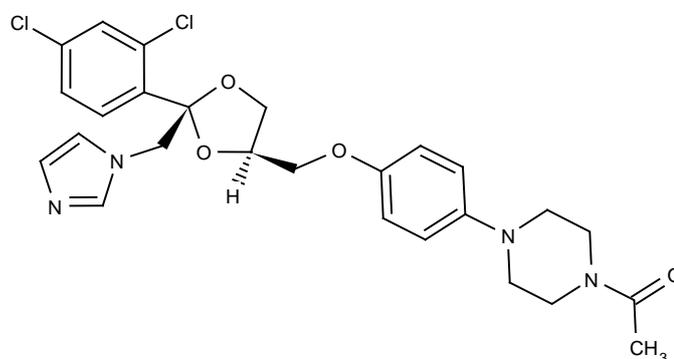


Figure 64. Structure of ketoconazole (CAS 65277-42-1, Mw 531.437).

Ketoconazole is usually prescribed for topical infections such as athlete's foot, ringworm, candidiasis (yeast infection or thrush), and jock itch. The over-the-counter shampoo version can also be used as a body wash for the treatment of tinea versicolor (Ortonne et al., 1992, Savin et al., 1986).

Ketoconazole is also used to treat eumycetoma, the fungal form of mycetoma. The side-effects of ketoconazole are sometimes used to treat non-fungal problems. For instance, the decrease in testosterone caused by the drug makes it useful for treating prostate cancer and for preventing post-operative erections following penile surgery (Evans et al., 2004).

Another use is the suppression of glucocorticoid synthesis, where it is used in the treatment of Cushing's disease. (Loli et al., 1986).

Ketoconazole can be prescribed as a 200-mg pill (ATC J02AB02), a 2% cream, a 2% gel, a 2% foam, or 2% shampoo for the treatment of dandruff or seborrhoeic dermatitis (ATC D01AC08), and also as a 1% over-the-counter shampoo (not accounted for in this study). In some countries also the 2% shampoo is sold over-the-counter. However not in the Nordic countries.

Ketoconazole is also available as a topical mousse, marketed under the brand name Ketomousse. Currently this formulation is not available in the Nordic countries.

Ketoconazole is structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a constituent of cell membranes, as well as certain enzymes. It is specific for fungi, as the equivalent mammalian pathway, leading to the biosynthesis of cholesterol, is not sensitive to ketoconazole (Liendo et al., 1999, Venkateswarlu and Kelly 1996). However, other mammalian cytochrome P450 enzymes can be sensitive to ketoconazole, and inhibition of steroid hormone synthesis is a possible side effect of ketoconazole treatment.

In a first attempt to assess the environmental impact of ketoconazole it can be concluded that aquatic plants are sensitive towards ketoconazole. *Selenastrum capricornutum* is so far the most sensitive species tested. A short-term  $EC_{50}$  (growth rate inhibition as endpoint) of 50  $\mu\text{g}$  results in a PNEC of 0.05  $\mu\text{g/l}$  (www.fass.se).

Furthermore, ketoconazole is not readily biodegradable (hence it does not fulfill the pass criteria of an OECD 301 test, www.fass.se). A somewhat complicating fact regarding the use of ketoconazole is that the substance is often used topically (on the skin), or as a component in soap and shampoo, therefore the fraction of the administered dose being subject to metabolism is expected to be insignificant. Furthermore, a great deal of the amount consumed can be anticipated to pass the WWTPs prior to reaching the environment.

Another possibly alarming finding is that ketoconazole may in fact potentiate the environmental effects of other types of xenobiotics. Hasselberg et al., have shown that juvenile rainbow trout exposed to a combination of ketoconazole and ethinyl estradiol experience an increased vitellogenin induction together with other enzymatic alterations in the juvenile fish, as compared with fish only exposed to ethinyl estradiol. The study demonstrated that exposure to ketoconazole compromised the function of key enzymes involved in metabolic clearance of xenobiotics and steroids, and increased the overall sensitivity to ethinyl estradiol exposure in juvenile rainbow trout (Hasselberg et al., 2008).

In order to assess the predicted environmental concentration of ketoconazole, contributions from the different formulations need to be summed. The tablet form of ketoconazole (ATC J02AB02) has a defined

daily dose of 200 mg which lends it to calculate the contribution to the PEC value. With regard to the other formulations of ketoconazole (shampoo, gels etc), at first a DDD of 300 mg was assigned based on an assumption of 15 ml of shampoo (20 mg/ml) being used every day. This exposure scenario is not totally unrealistic but after lengthy discussions a scenario based on using the shampoo twice a week, using only 10 ml, yields a DDD of 60 mg. In some manufacturer's PILs (Patient Information Leaflet) on ketoconazol the patients are instructed to initially use the shampoo 2–3 times a week, and as the symptoms are being relieved, only use the shampoo once every second week ([www.fass.se](http://www.fass.se)). Thus, a DDD of 300 mg, as initially suggested for ATC D01AC08 seems unrealistically high, rendering ketoconazole to be one of the really high risk pharmaceuticals in this study. Therefore, the project has used the DDD of the exposure scenario, 60 mg for ATC D01AC08.

#### 4.1 Ketoconazole in Denmark

In Denmark 11.7–15.3 kg/year of ketoconazole is being sold as pills (ATC J02AB02) while the consumption of the other formulations is estimated to be between 890–1100 kg/year (DDD of 60 mg), during the period 1997–2007. Thus, the load of ketoconazole stemming from the pills amounts to 1–1.5 % of the total load (see Figure 65. Together with Sweden, Denmark shows an overall consumption of ketoconazole one order of magnitude higher than the other Nordic countries (relative to the population).

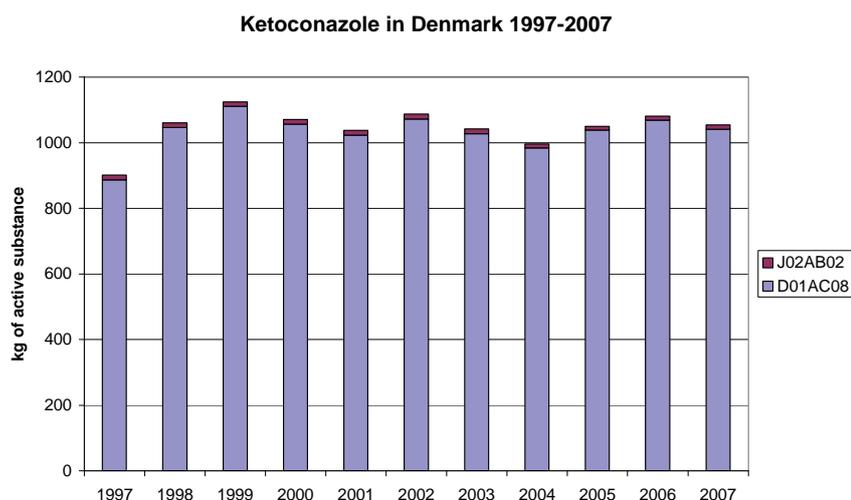


Figure 65. Consumption of ketoconazole in Denmark 1997–2007 (two ATC groups included).

## 4.2 Ketoconazole in Finland

The Finnish dataset did not include the ATC group D01AC08 (being the major contributor to the overall PEC) and therefore it is of marginal value to further compare the Finnish data with the other Nordic countries. However, it can be concluded that the ketoconazol consumption in pill formulations are 60–70 % higher in Finland, compared to Denmark, despite the fact that the countries are of almost equal population (see Figure 66).

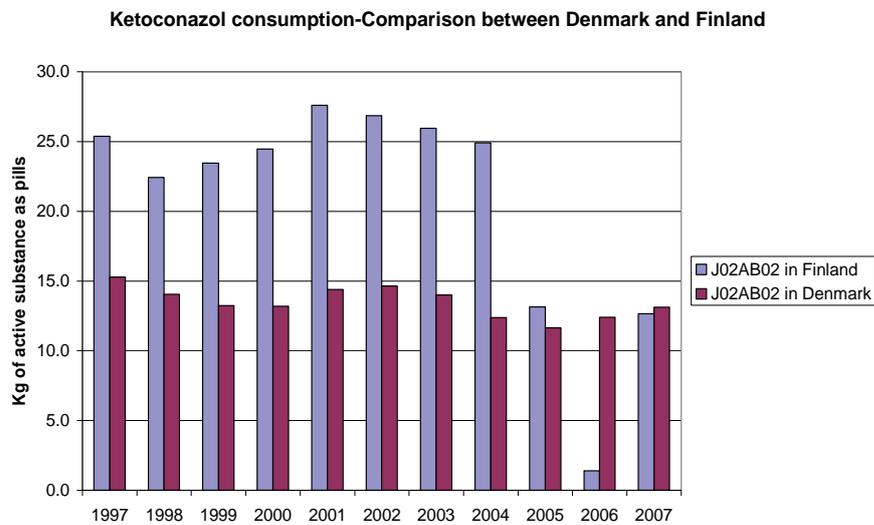


Figure 66. Comparison between Ketoconazole consumption in Denmark and Finland (only tablets formulations are included, ATC J02AB02)

## 4.3 Ketoconazole in Sweden

In the Swedish data set on ketoconazol, data was available for every second year (1997, 1997, 2001, 2003, 2005 and 2007). Linear interpolation has been used to generate the “missing” years. It can be concluded that also in Sweden, the non-tablets formulation (ATC D01AC08) represents 98–99.5 % of the total sales of ketoconazol. Pills (ATC J02AB02) varied between 12–19 kg/year during the period, while “shampoos” (ATC D01AC08) varied between 1220–1772 kg/year (see Figure 67).



Figure 67. Ketoconazole sold in Sweden 1997–2007 (two ATC groups included).

#### 4.4 Ketoconazole in Norway

In Norway, very much in contrast to the other Nordic countries where data was available, consumption of ketoconazole in pills contributed significantly to the overall consumption (12–31 %). Consumption of ketoconazole in “shampoos” (32–68 kg, ATC D01AC08) seems to be a factor of 10–15 lower than what can be expected (taking also the population size into consideration, see Figure 68).

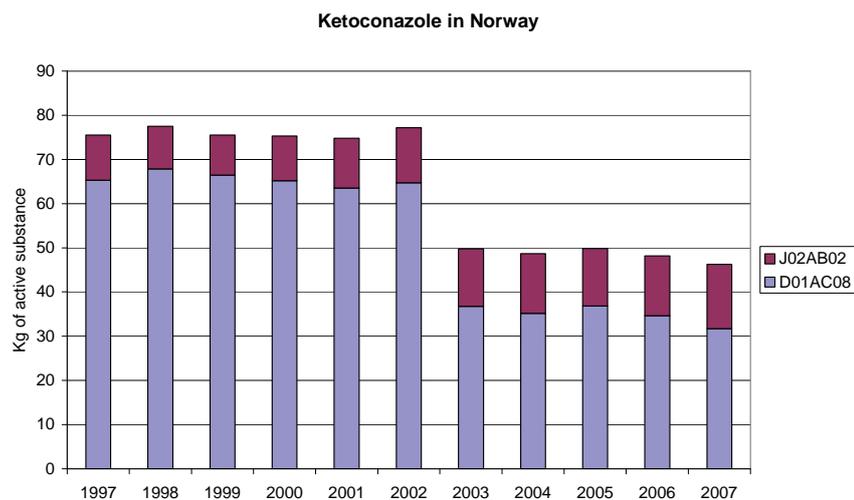


Figure 68. Ketoconazole sold in Norway 1997–2007 (two ATC groups included).

## 4.5 Ketoconazole on Iceland

The Icelandic data were parameterized down to each individual brand on the Icelandic market during the period and hence the accuracy of the data seems indubitable.

As can be seen in Figure 69, Iceland resembles Norway in the consumption pattern of ketoconazole; ketoconazole from pills constitute 16–36 % of the total sales. Furthermore, the consumption of ketoconazole-based shampoos, gels and creams is steadily decreasing while the amount consumed as pills seem constant (similar pattern in Norway, Figure 68).

Pills (ATC J02AB02) varied between 0.7–1 kg/year during the period, while “shampoos” (ATC D01AC08) varied between 1.5–5 kg/year (Figure 69).

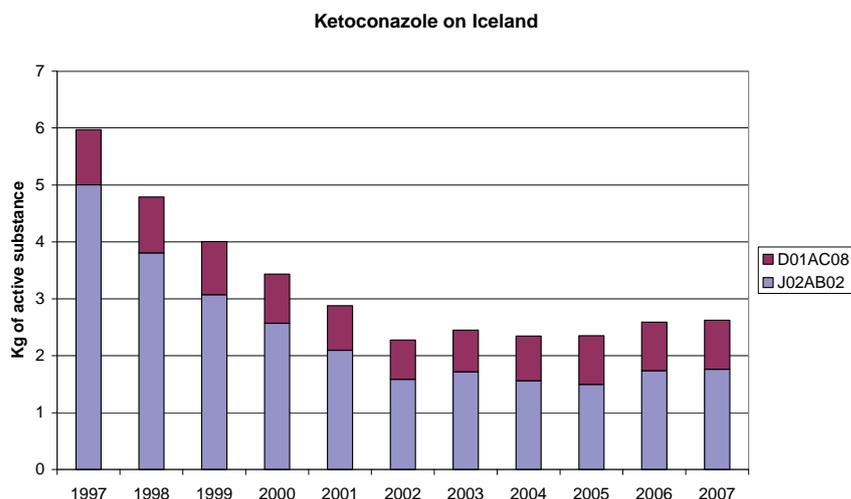


Figure 69. Ketoconazole sold on Iceland 1997–2007 (two ATC groups included).

## 4.6 Predicted environmental concentration of ketoconazole in the Nordic countries

As can be seen in Figure 70 Sweden and Denmark stands out as having a high level of ketoconazole consumption, compared with the other Nordic countries. The situation in Finland is however a bit unclear still, since no data on ATC D01AC08 was available to the project.

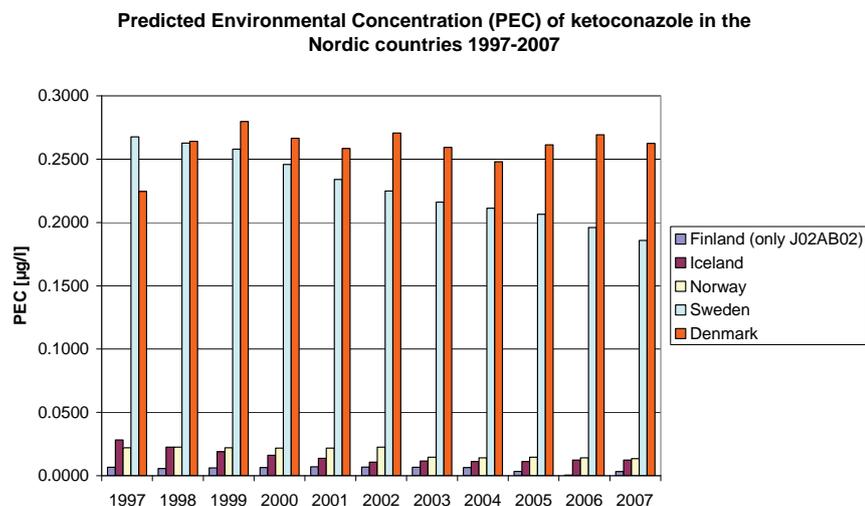


Figure 70. PEC values of ketoconazole in the Nordic countries.

#### 4.7 Environmental risk assessment of ketoconazole in the Nordic countries.

In accordance with the calculated PEC values of ketoconazole, environmental risk quotients (PEC/PNECs) are easily calculated. It can be concluded that current consumption levels in Sweden and Denmark pose an environmental risk ( $PEC/PNEC \gg 1$ ) while in Norway and Iceland ketoconazole pose an insignificant environmental risk. In Finland, where sales data on non-pill formulations were lacking, the environmental risk from ketoconazole is probably 10–100 times higher than illustrated in Figure 71.

Regarding possible mitigating factors such as fast biodegradation kinetics or high removal rate in the WWTPs, ketoconazole is not readily biodegradable (OECD 301F) and the average removal rate in a typical Nordic WWTP is not known.

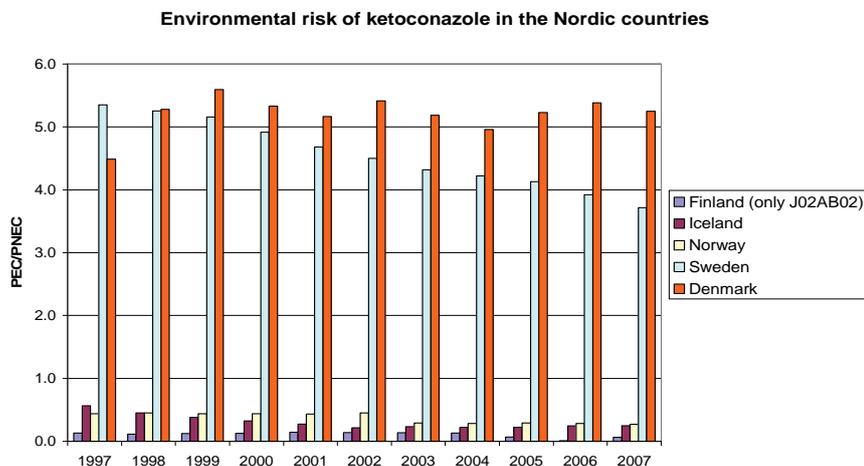


Figure 71. Environmental risk quotients of ketoconazole in the Nordic countries 1997–2007.

## 4.8 Accumulated environmental risk of ketoconazole in the Nordic countries

Since ketoconazole does not seem to be readily biodegradable the issue of accumulation in the environment may turn out to be an important issue for consideration in the environmental risk assessment. Ketoconazole has in this study been assigned as *persistent* (i.e., 80% of the sold amount year 1 is considered as remaining year 2). From Figure 72 it is evident that the environmental risk quotient of ketoconazole is increasing when taking the persistence into consideration. In Sweden, the total sale of ketoconazole has decreased by 30 % over the period 1997–2007 (Figure 71). However, the accumulated environmental risk has increased with 72 % during the same period (Figure 72).

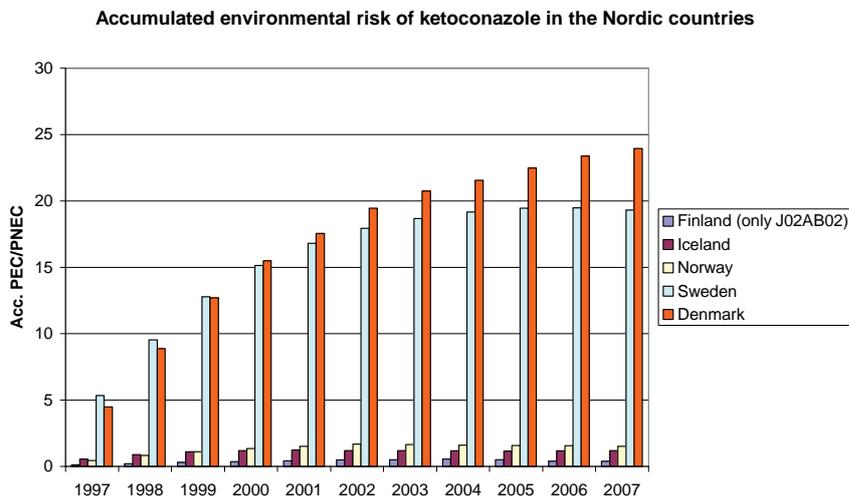


Figure 72. Accumulated environmental risk of ketoconazole in the Nordic countries 1997–2007. Ketoconazole has been regarded as persistent in this calculation.

## 5. Triclosan, a suitable risk assessment marker substance for pharmaceuticals?

Early on when planning for this investigation, the use of a non-pharmaceutical type of substance to compare calculated environmental risks with emerged. Ideally, such a substance should share the same dispersion pathway as pharmaceuticals have; from the consumer (the patient) through the sewage system-the waste water treatment plant to the receiving water recipients. One such emerging pollutant is triclosan. Triclosan (*IUPAC name*: 5-chloro-2-(2,4-dichlorophenoxy)phenol) is a potent wide spectrum antibacterial and antifungal agent. The main use of triclosan is in products such as toothpastes, soaps (0.15–0.30%), deodorants, shaving creams, mouth washes, and cleaning supplies. It has also been infused in an increasing number of consumer products, such as kitchen utensils, toys, bedding, socks, and trash bags. Triclosan has been shown to be effective in reducing and controlling bacterial contamination on the hands and on treated products. For instance, showering or bathing with 2% triclosan has become a recommended regimen for the decolonization of patients in the US whose skin is carrying methicillin resistant *Staphylococcus aureus* (MRSA) following the successful control of MRSA outbreaks in several clinical settings (Brady et al., 1990, Zafar et al., 1995).

As a biocide triclosan is toxic in itself and the environmental fate of triclosan has been thoroughly investigated. Moreover, the use of triclosan in household anti-bacterial products introduces the chemical to surface waters where it can form dioxins (Rule et al., 2005). Also speculations on whether triclosan overuse could cause resistant strains of bacteria to develop, in much the same way that antibiotic-resistant bacterial strains are developed, have emerged. The issue seems to be rather complex since some bacteria like *Escherichia coli* and *Staphylococcus aureus* may gain a “low-level” resistance to triclosan (Heath et al., 1999, and Fan et al., 2002). These speculations on a general development of resistant bacteria strains have not proven to be correct so far however (McBain et al., 2003, and Aiello et al., 2004, Yazdankhah et al., 2006), but have caused triclosan to become a substance of concern and phase-out in the Nordic countries.

To assess the environmental risk associated with current levels of triclosan use the SPIN database on the use of substances in products in the Nordic Countries was utilized. The database is based on data from the Product Registries of Norway, Sweden, Denmark and Finland (financed by the Nordic Council of Ministers, Chemical group). (<http://195.215.251.229/>

fmi/xsl/spin/SPIN/maininfo.xsl?-db=SPINstof&-lay=SpinNavn&-max=1&-findall).

When comparing estimated turn-over figures for certain chemicals in the SPIN registry database it is important to note that in the Nordic countries triclosan data mostly refers only to the raw material and not to products containing triclosan (data from Denmark until 2000 also contained product classes like cosmetics and hygiene products). Hence, the total turn over may in fact be several times higher than data from SPIN suggests.

For instance, triclosan used in imported cosmetics and cosmetic products are not included, while triclosan as a pure substance being used for the domestic production of cosmetic products is included.

In Sweden, SPIN data on triclosan does contain several product categories, apart from raw materials, when the triclosan content is above 0.0025 % (w/w). However, cosmetics and hygiene products as such, is not included among the product categories listed.

According to the Chemicals Agency in Sweden (KemI), the overall trend in Sweden is a decline in the import of triclosan (5.2 tonnes in 1999 to 2.9 tonnes in 2003). During the same period the export of triclosan (and triclosan containing products) out of Sweden have decreased even more and the conclusion is therefore that the use of triclosan and triclosan-containing products have increased in Sweden during the period (<http://www.kemi.se/templates/Page.aspx?id=3736>).

In a report by the Swedish Medical agency (Läkemedelsverket, 2004) the annual turnover and use of triclosan in Sweden was estimated to be 2.76 tonnes in 2002, which corroborates the data from the Swedish Chemicals Agency.

From SPIN data on volumes used (covering the period 1999–2006) and chronic aquatic toxicity data (see table below), National PEC/PNEC-quotients were calculated.

**Table 2. Ecotoxicological data on triclosan from Orvos et al., 2002 (courtesy of Mats Allmyr, ITM, Sthlm).**

Taxa	Species	Duration	Endpoint	Value (µg/L)	Comment
Fish	<i>Onkorynchus mykiss</i>	61 d	NOEC	<b>34</b>	Hatchability and fry survival
Invertebrate	<i>Cerodaphnia dubia</i>	7 d	NOEC	<b>6</b>	Survival and reproduction
Algae	<i>Scenedesmus subspicatus</i>	3 d	NOEC	<b>0.5</b>	Growth

Assessment of PEC/PNEC-quotients of triclosan in the Nordic countries 1999–2006, from data entries in the SPIN database (KemI).  
PNEC-value of 0.05 µg/l used (based on 3d growth NOEC on algae *Scenedesmus subspicatus* (Orvos et al., 2002).

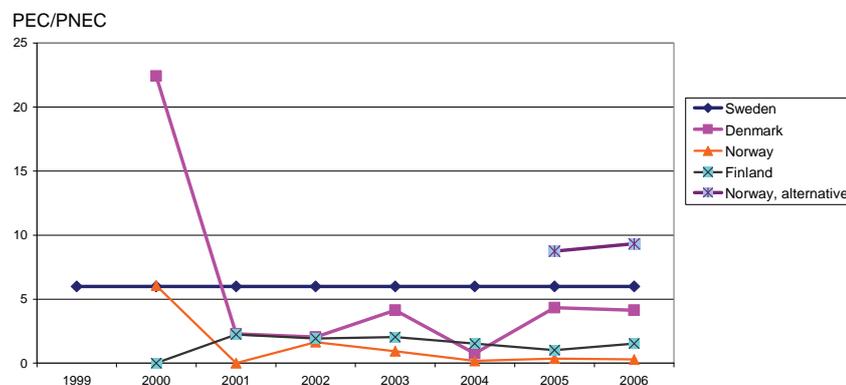


Figure 73. Consecutive PEC/PNEC risk assessment of the use of triclosan in the Nordic countries 1996–2006. SPIN data on triclosan use in Sweden have been constant, 2 000 kg annually. The alternative trace for Norway (only 2005–2006) corresponds to estimates of the total circulation of the substance (from a report from SFT in 2009) and in that calculation also the fraction originating from cosmetics have been assessed.

From Figure 73 it is evident that triclosan, being mainly dispersed to the environment through consumer use and then subsequent migration through the sewage system, have similar PEC/PNEC-quotients as the intermediate-high segment of pharmaceuticals. Thus, using triclosan as a comparative marker for environmental risk as compared with human pharmaceuticals may not be so far-fetched.

The great uncertainties associated with the SPIN data on triclosan must be emphasized however. For instance, SPIN data from Norway suggests an annual triclosan turn-over of 1.04 tonnes in the year 2000 and then a rapid decline down to only 50 kg in 2006. When disseminating these figures and comparing with other available data from other sources (<http://www.sft.no/publikasjoner/2494/ta2494.pdf>), the turn-over part from cosmetics alone seem to contribute to 1.5 tonnes in 2005 and 2006. This would then add up to a Norwegian PEC/PNEC of 9.3 for the years 2005–2006. The current debate regarding the actual risk-benefit of adding triclosan to consumer products can be anticipated to significantly decrease the annual use of triclosan in then Nordic countries in the future.

In an attempt to re-calculate PEC/PNEC data on the use of triclosan in Sweden (rather than the reported import, available through SPIN), data from KemI, the Swedish Chemicals Agency (see web link), suggests that the use of triclosan in Sweden (import-export) increased steadily until 2004, and after that year the usage figures have decreased, probably due to the publicity that triclosan has gained in environmental science (Figure 74). The re-calculated data supports the notion of a national PEC/PNEC for triclosan in Sweden of 5–10.

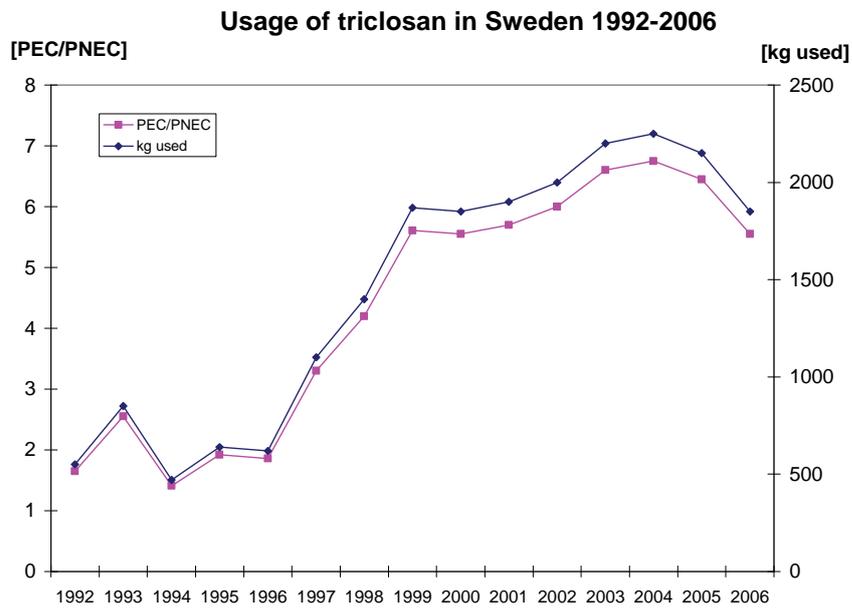


Figure 74. Re-calculated use (right ordinata) and corresponding PEC/PNEC (left ordinata) of triclosan in Sweden 1992–2006.

## 6. Environmental risk associated with certain Modes-of-Actions (*'across a therapeutic class'*)

In an attempt to visualise how a therapeutic class of pharmaceuticals, rather than single drugs, may influence the aquatic environment, this study have suggested to calculate a “Mode-of-action-based” environmental risk quotient. The rationale behind this concept resides in the fact that several drugs belonging to the same therapeutic class most often target the very same biological receptor in the human body, and hence also possess similar ecotoxicological properties. Oftenly, the pharmaceuticals belonging to the same therapeutic class have several structural traits in common such as certain functional groups. If these drugs are only risk assessed individually, one-by-one, the reviewer might in fact miss the apparent, summed ecotoxicological pressure that a cocktail of these drugs discharged into a recipient may induce.

As an illustrative example the therapeutic class of proton pump inhibitors were chosen. Proton pump inhibitors are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today. The group followed and has largely replaced another group of pharmaceuticals with similar effects, but different mode-of-action, called H<sub>2</sub>-receptor antagonists. These drugs are among the most widely-selling drugs in the world as a result of their outstanding efficacy and safety (Kaiser Family Foundation, 2005). Structurally, the vast majority of these drugs are benzimidazole derivatives (Sachs, 2006).

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H<sup>+</sup>/K<sup>+</sup> ATPase, or more commonly just gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H<sup>+</sup> ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.

Targeting the terminal-step in acid production, as well as the irreversible nature of the inhibition, result in a class of drugs that are significantly more effective than H<sub>2</sub> antagonists and reduce gastric acid secretion by up to 99%.

The proton pump inhibitors are given in an inactive form. The inactive form is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. In an acid environment, the inactive drug is

protonated and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

As can be seen in the structural formulas below (Figure 75), these drugs are in fact structural analogues (common structural motif in the green frame). As structural analogues they may in fact all possess a common toxicophore and thus a common ecotoxicological mode of action.

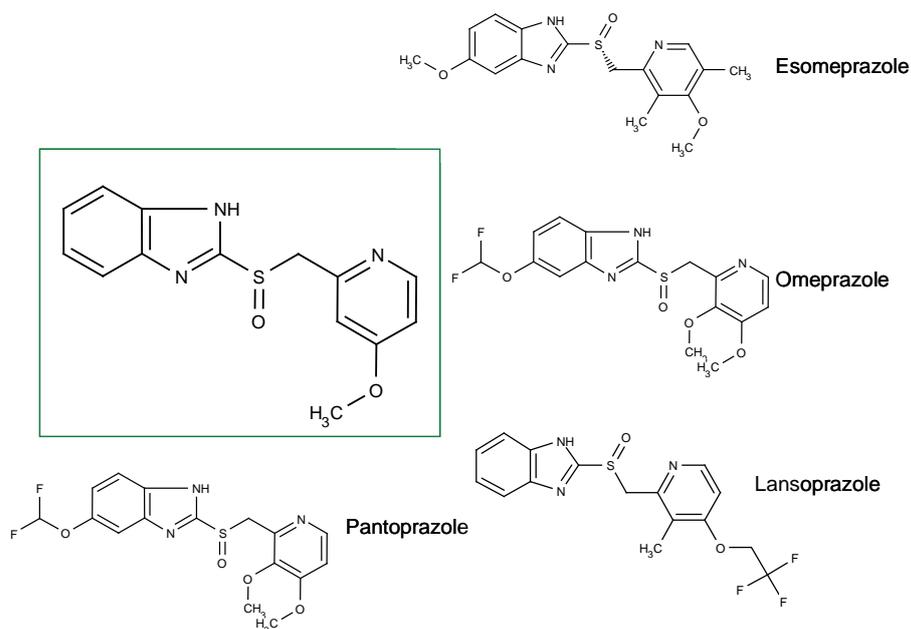


Figure 75. Structural features of common proton pump inhibitors. The common motif and chemical functionality is given in the green frame.

When the sales pattern of the proton pump inhibitors (PPIs) are displayed it is obvious that the consumption levels (with respect to number of inhabitants) are almost identical in Norway, Denmark and Finland. In Sweden and Iceland, on the other hand, there is a rapid increase in the consumption in the beginning of the period 1997–2002 and hence at the end of the period the summed PECs of the PPIs are twice as high in Sweden and on Iceland 0.9–1 µg/l, compared with 0.4–0.5 µg/l).

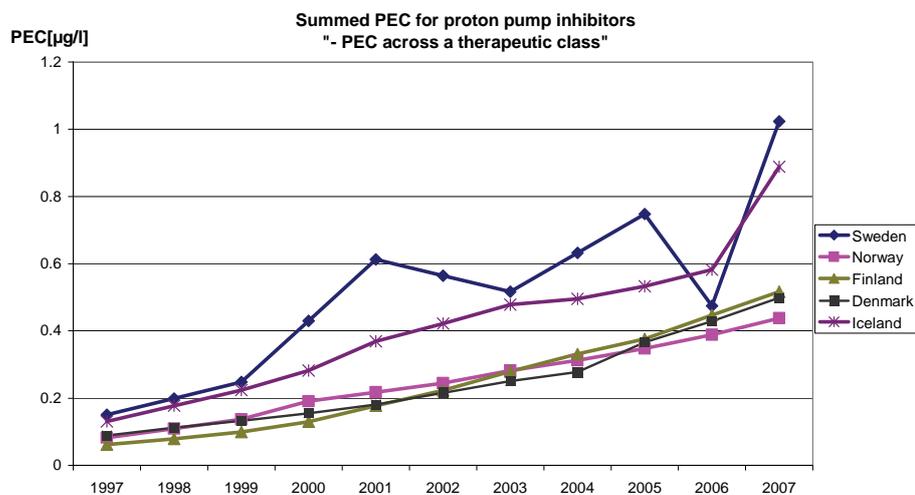


Figure 76. Summed PECs across a therapeutic class of drugs; proton pump inhibitors.

In all Nordic countries, omeprazole is the major PPI substance on the markets. In November 2000 the enantio-pure version of omeprazole, esomeprazole, was granted market admission (omeprazole being a racemate of two enantiomers) and from 2001 there is sales statistics also for esomeprazole. In most countries one can observe a decline in the sales of omeprazole accompanying the rapid sales increase of esomeprazole in the years 2001–2003. In Figure 77 the summed quantities of esomeprazole and omeprazole are displayed for the Nordic countries. As can be seen, sales in Sweden have increased by 63 % (from 1 tonne in 1997 to approximately 2.5 tonnes in 2007). In Denmark, and Norway the consumption has increased in a similar fashion (74–77 %), while the sales increase in Finland and on Iceland amounts to 89–90%, respectively (Figure 77).

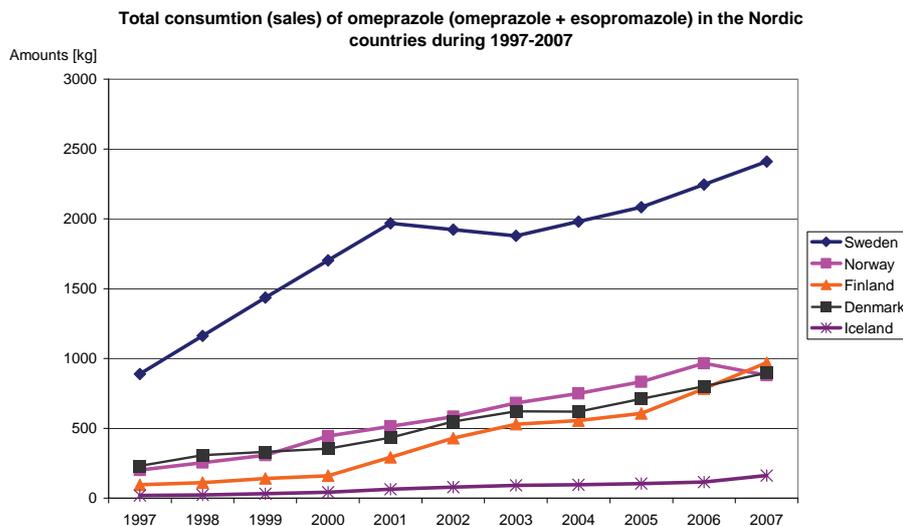


Figure 77. Quantities sold of omeprazole and esomeprazole in the Nordic countries 1997–2007.

Also concerning omeprazole and esomeprazole calculated PECs show that the relative consumption is highest on Iceland and in Sweden compared to the situation in Denmark, Finland and Norway (Figure 78).

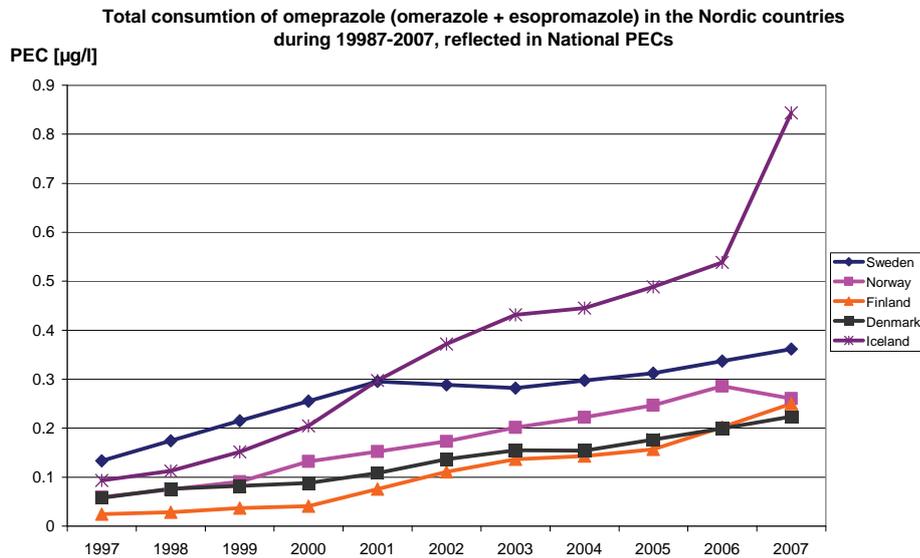


Figure 78. PEC-values of omeprazole and esomeprazole in the Nordic countries 1997–2007.

When discerning the environmental risks associated with the use of PPIs it is important to note that the ecotoxicity tests and the corresponding NOEC-, EC<sub>50</sub> or even LC<sub>50</sub>-values reflect acute toxicity testing and that PPIs may in fact also trigger receptors in aquatic organisms that regulate the proton flux in lumen (an endpoint not covered by standard acute toxicity testing).

In Figure 79 the summed environmental risk for the total therapeutic PPI class (pantoprazole, lansoprazole, omeprazole and esomeprazole) for each Nordic country is displayed as a function of time. From the plot it is evident that PPIs do not impose any environmental risk (risk quotients < 1) but it is also evident that taking the sum of all the PPI consumption also reveals an increase in the environmental risk by a factor of ten in Sweden (for instance) during the period while calculating the risk for a substance at the time would not reveal that fast increase in the risk.

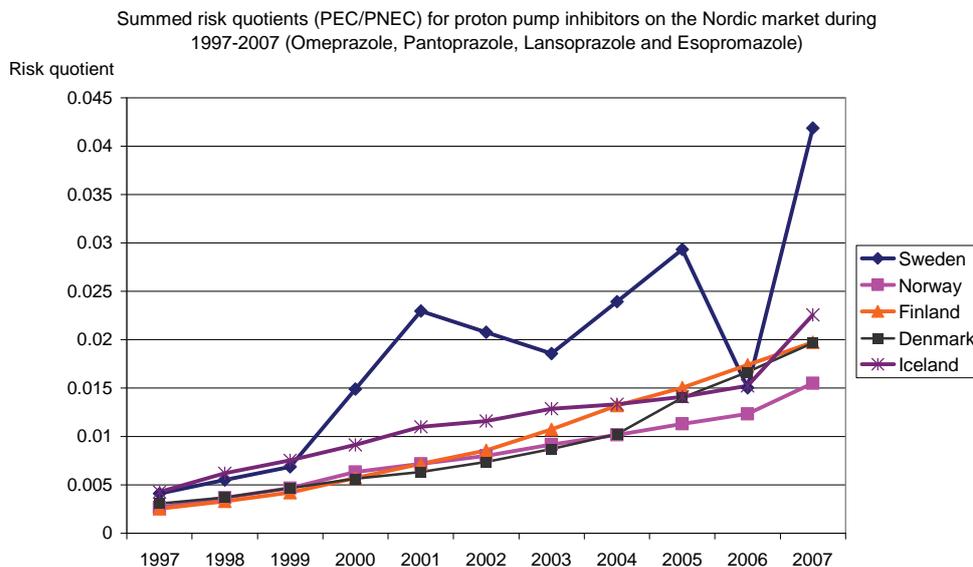


Figure 79. The summed environmental risk for the total therapeutic PPI class (pantoprazole, lansoprazole, omeprazole and esomeprazole) for each Nordic country is displayed as function of time.

Similarly to the proton pump inhibitors, the same type of re-calculation of environmental risk based on summation of a therapeutic class have been made for the SSRI drugs.

Selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitor (SSRIs) are a class of compounds typically used as antidepressants in the treatment of depression, anxiety disorders, and some personality disorders. They are also typically effective and used in treating premature ejaculation problems as well as some cases of insomnia. SSRIs increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with pure SSRIs having only weak affinity for the noradrenaline and dopamine transporter.

In the figures below (Figure 80, Figure 82) the consumption of most common SSRI pharmaceuticals on the Nordic market have been included; fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine.

Summed Nordic consumption of SSRI-pharmaceuticals N06AB (Citalopram, Escitalopram, Sertraline, Paroxetine, Fluoxetine and Fluvoxamine) in the Nordic countries 1997-2007.

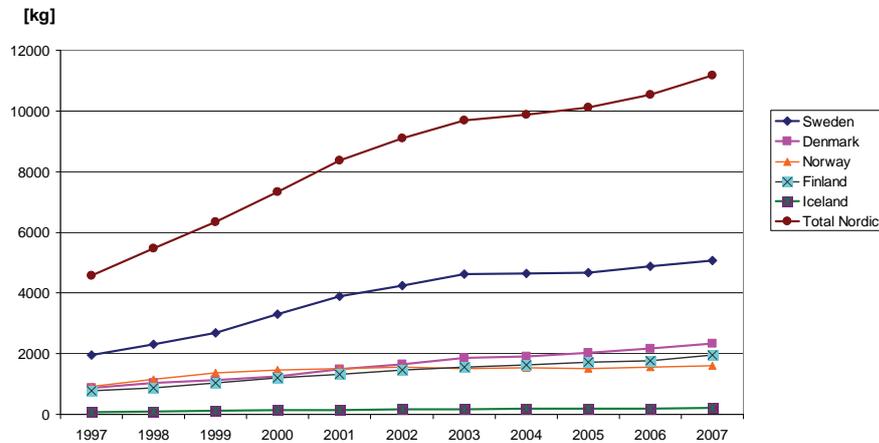


Figure 80. Overall consumption of the therapeutic class of SSRI drugs in the Nordic countries 1997-2007.

From Figure 80 it is evident that Sweden accounts for approximately 50 % of the total Nordic SSRI-consumption and that the consumption in Denmark, Finland and Norway seems to be virtually identical.

In the data set of SSRI drugs sold in the Nordic countries the environmental risk with respect to each individual country has been studied (as for instance is displayed in Figure 81). Normally the highest risk quotients for SSRI drugs are retrieved from Sweden and Iceland but in the case of fluoxetine the relative amount consumed/sold in Finland seems high. Possibly, the fluoxetine share of the Finnish SSRI market is higher than the corresponding market share in the other countries.

Environmental risk associated with the SSRI pharmaceutical Fluoxetine in the Nordic countries 1997-2007.

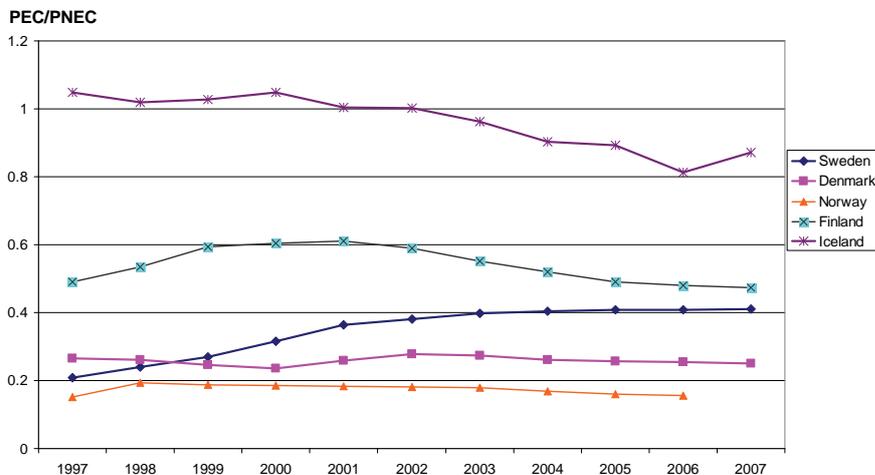


Figure 81. The environmental risk associated with the SSRI drug fluoxetine, displayed for each country.

Finally, in Figure 82, the summed environmental risk across the whole therapeutic SSRI class is displayed (for all Nordic countries), as a function of time. It is evident from the logarithmic ordinate axis that sertraline accounts for > 87 % of the total therapeutic environmental risk (in 2007) while the sales of sertraline in the Nordic countries that year accounted for less than 38 % of the total mass of SSRIs sold (in kg, 2007). Measures taken which are directed at reducing the environmental stress posed by SSRI drugs should therefore be directed primarily towards sertraline (*i.e.* changing the prescription pattern, optimising STP operations *etc.*).

**Summed environmental risk associated with sales of SSRI - pharmaceuticals in the Nordic Countries, 1997-2007**

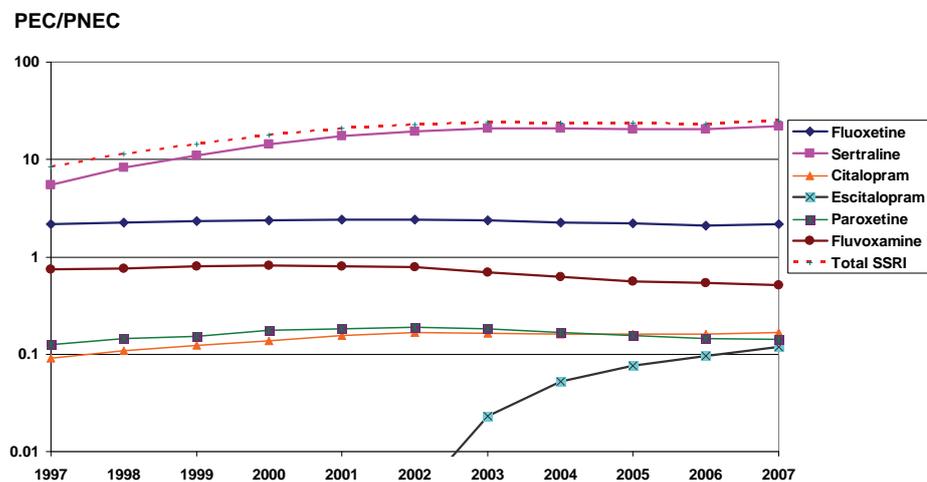


Figure 82. The summed environmental risk for the total therapeutic SSRI class (fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine) for all Nordic countries is displayed as function of time. Please, note that the ordinate axis is logarithmic.



## 7. Conclusions

The most important conclusion from this elaborate study of consumption pharmaceuticals in the Nordic countries and the corresponding environmental risks is that the consumption patterns between the different countries are very much alike; the “top30” PEC list is almost identical in the throughout Scandinavia, as is the “top30” PEC/PNEC-lists, as well as the accumulative-PEC/PNEC-lists.

This is an important conclusion since then mitigating actions, regulatory policies, information campaigns to the general public, and further national research can be directed in the same general direction in the Nordic countries. Co-operation between Nordic countries in the dissemination of these issues is thus rational and required.

There are reasons to believe that this report may also be of use in the selection of pharmaceuticals for environmental screening efforts. In the top PEC/PNEC lists presented herein there are in fact several drugs that have not yet emerged as target substances in Nordic screening studies.

Except for Ketoconazole (in Denmark and Sweden), the top PEC/PNEC-candidates disseminated in the different countries were very much the expected ones; hormones, diclofenac, paracetamol and sertraline.

There is an almost complete trend towards increasing consumption and sales of most pharmaceuticals in the Nordic countries. Over a period of ten years (1997–2007) 45 of the 60 top-selling pharmaceutical formulations in Sweden showed an increased consumption of 49 % (as a median value), in 5 cases were the consumption level constant, and in 10 cases a decreased consumption could be noticed (32 % as a median value). Thus, the environmental risks can be expected to have increased in a corresponding way. However, these risk data mostly represents a worst case scenario. Metabolism in the patient eating the medicine, degradation in the sewage system, removal in the STP and further biodegradation in the environment may reduce the actual concentration reaching the environment. Furthermore, a fraction of the sold amount of pharmaceuticals will never be consumed. Instead that fraction is likely to end up in the recycling bin or being flushed down the sewer. In all Nordic countries there are well-organised and rational take-back schemes for unused drugs (anybody can leave their unused drugs at any local pharmacy for incineration rather than flushing down unused drugs in the toilet). However, it is difficult to assess the importance of the Nordic take-back schemes on pharmaceuticals (the tonnage of pure substance being returned to the pharmacies).

Since data on these mitigating factors are seldom publicly available it is difficult to take them into consideration. PEC/PNEC-quotients of 20–

70 seem alarmingly high and might very well be reduced if metabolism and STP-removal were taken into account.

The suggested use of “Accumulated” PEC/PNECs to also account for possible build-up in the environment due to slow biodegradation is still in the concept stage and the exact boundaries between different classes of biodegradation kinetics, which in this report is more *ad hoc* (persistent, slowly, inherent, ready), needs of course to be further corroborated by experimental measurements. However, at the current level of knowledge pharmaceuticals (*in general*) seem less prone to biodegrade than common organic chemicals (*in general*) and the “Accumulated” PEC/PNECs may therefore serve as a “worst case scenario”, complementing the yearly based PEC/PNEC risk assessment (where the general assumption is that everything released into the environment year  $x$  is biodegraded prior to the release year  $x+1$ ).

The “Accumulated” PEC/PNECs are in some cases alarmingly high, as in the case of the estrogens and their corresponding PEC/PNECs in the vicinity of 100 suggests that in some Nordic recipients where the STP discharges are not diluted by as much as a factor of ten (as stipulated in Eq. 2 and 3), it is very probable that aquatic species are in fact already affected.

However, it is important to keep in mind that several of the pharmaceuticals classified as “*potentially persistent*” in the “accumulated PEC/PNEC figures (50 out of ca 90 pharmaceuticals herein, see table in *Appendix 1*) have a persistence classification based on “*lack of data*”. In yet ten other cases, there are ambiguities in the fass.se dataset (one company classifies the drug as persistent while another company classifies it as *inherently* or *slowly biodegradable*). In 30 cases though, experimental data on fass.se merit the classification “*potentially persistent*”.

In an attempt to compare Nordic environmental risk assessment quotients of human pharmaceuticals with other chemicals primarily being used by private consumers a comparison with the biocide triclosan was made. Since triclosan is a biocide used in cosmetics and tooth paste and thus entering the sewage system after use, rendering it a pattern of disposal similar to the pharmaceuticals (“down-the-drain usage”), it was considered appropriate for the purpose of comparison. PEC/PNECs for triclosan in the Nordic countries well exceeded unity in most of the countries and can be expected to be even higher (uncertainties in the quality of the import-export data from the SPIN database, the exclusion of cosmetics etc, renders it difficult to use SPIN data). The PEC/PNEC quotients of several pharmaceuticals were comparable with (or even exceeded) the quotients calculated for triclosan in the Nordic countries (when compared with Swedish and Norwegian data).

Furthermore, the concept of environmental risk assessment across a therapeutic class of pharmaceuticals may prove useful. This approach could be utilized especially in cases where receptor interactions as such and/or

structural resemblance (between the drugs within the class) make it plausible that similar effects can be anticipated from several, different pharmaceuticals (as in the case of the SSRI drugs or the proton pump inhibitors).



## 8. References

- Abu-Fanne R, Brzezinski A, Golomb M, Grad E, Foldes AJ, Shufaro Y, Varon D, Brill A, Lotan C, Danenberg HD (2008). "Effects of estradiol and raloxifene on arterial thrombosis in ovariectomized mice". *Menopause*, Jan-Feb;15(1):98–104
- Aiello A E, Marshall B, Levy S B, Della-Latta P, Larson E (2004). "Relationship between triclosan and susceptibilities of bacteria isolated from hands in the community". *Antimicrob. Agents Chemother.* 48 (8): 2973–2979.
- Andersson J, Woldegiorgis A, Remberger M, Kaj L, Ekhedén Y, Dusan B, Brorström-Lundén E (2006). "Results from the Swedish National Screening programme 2005, Subreport 1: Antibiotics, Anti-inflammatory substances and Hormones". September 2006, IVL B1689.
- Ashton D, Hilton M, Thomas K.V. (2004). "Investigating the environmental transport of human pharmaceuticals to streams in the United Kingdom." *Science of the total Environment*, vol 333, pp 167–184.
- Bersch, M., 1995: On the circulation of the northeastern North Atlantic. *Deep-Sea Research Part I*, 42, 1583–1607.
- Brady L M, Thomson M, Palmer M A, Harkness J L (1990). "Successful control of endemic MRSA in a cardiothoracic surgical unit". *Med. J. Aust.* 152 (5): 240–245.
- Brian JV, Harris CA, Scholze M, Kortenkamp A, Booy P, Lamoree M, Pojana G, Jonkers N, Marcomini A, and Sumpter JP, (2007). Evidence of estrogenic mixture effects on the reproductive performance of fish. *Environmental Science and Technology*, 41(1), 337–344.
- Borenstein E, Shlomi T, Ruppin E, Sharan R. (2007). "Gene loss rate: a probabilistic measure for the conservation of eukaryotic genes". *Nucleic Acids Research*, vol 35(1).
- Collaborative Group on Hormonal Factors in Breast Cancer (1996). "Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies". *TheLancet.* Jun 22;347(9017):1713–27
- Coronado J E, Mneimneh S, Epstein S L, Qiu W-G, Lipke P N. (2007). "Conserved Processes and Lineage-Specific proteins in Fungal Cell Wall Evolution". *Eukaryotic Cell*, vol Dec., pp 2269–2277.
- Costanzo, S.D., J. Murby and J. Bates. (2005) Ecosystem response to antibiotics entering the aquatic environment. *Marine Pollution Bulletin* 51:218–223.
- Cleuvers, Michael. (2003). "Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects". *Toxicology Letters*, Volume 142, Issue 3, 15 May 2003, Pages 185–194.
- Data on use of triclosan in Sweden, from KemI, the Swedish Chemicals Agency, (<http://www.kemi.se/templates/Page.aspx?id=3736>).
- Diana S. Aga, "Fate of Pharmaceuticals in the Environment and in Water Treatment Systems", 12/26/2007, 408 pages, ISBN: 9781420052329, CRC
- Daughton Christian G and Ternes Thomas A. (1999). "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change", *Environmental Health Perspectives*, Vol 107, Supplement, December, pp 907–938.
- EU technical guidance document (TGD), European Commission 2003. Technical guidance document in support of Commission Directive 93/67/EEC on Risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on Risk assessment for existing substances and Commission Directive (EC) 98/8 on biocides, second ed. European Commission, Luxembourg, Part 1, 2 and 3, 760pp.
- Evans, K. C.; A. C. Peterson, H. E. Ruiz and R. A. Costabile (August 2004). "Use of oral ketoconazole to prevent postoperative erections following penile surgery". *International Journal of Impotence Research* 16 (4): 346–349
- Fan F, Yan K, Wallis N G, et al. (2002). "Defining and combating the mecha-

- nisms of triclosan resistance in clinical isolates of *Staphylococcus aureus*". *Antimicrob. Agents Chemother.* 46 (11): 3343–3347.
- Fent K, Weston AA, Caminada D. (2005). "Ecotoxicology of human pharmaceuticals", 1: *Aquat Toxicol.* 2006 Feb 10;76(2):122–59.
- Ferrari, B., R. Mons, B. Vollat, B. Fraysse, N. Paxeus, R. Lo Giudice, A. Pollio and J. Barric. (2004) Environmental risk assessment of six human pharmaceuticals: are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? *Environmental Toxicology and Chemistry* 23(5):1344–1354.
- Ferrari, B., N. Paxeus, R. LoGuidice, A. Pollio, and J. Garric. (2003) Ecotoxicological impact of pharmaceuticals found in treated wastewaters: study of carbamazepine, clofibrac acid and diclofenac. *Ecotoxicology and Environmental Safety* 55:359–370.
- "Follow The Pill: Understanding the U.S. Commercial Pharmaceutical Supply Chain". The Health Strategies Consultancy LLC, for the H. Kaiser Family Foundation. March 2005.
- Gibs Jacob, Stackelberg Paul E, Furlong Edward T, Meyer Michael, Zaugg Steven D, Lee Lippincott Robert, (2007). "Persistence of pharmaceuticals and other organic compounds in chlorinated drinking water as a function of time", *Science of the total environment*, vol. 373, no1, pp. 240–249.
- Grung M, Källqvist T, Sakshaug S, Skurtveit S, Thomas K. V. (2008). "Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline." *Ecotoxicology and Environmental Safety*, vol 71(2), 328–340.
- Gunnarsson L., Jauhiainen A., Kristiansson E., Nerman O. and Larsson D.G.J. (2008). "Evolutionary conservation of human drug targets in organisms used for environmental risk assessments". *Environ. Sci. Technol.*, Volume 42 (15), pp 5807–5813.
- Guideline on the environmental risk assessment of medicinal products for human use., EMEA, Doc. Ref. EMEA/CHMP/SWP/4447/00, London, 01 June 2006.
- Halling-Sørensen, B., S. Nors Nielsen, P. F. Lanzky, F. Ingerslev, H. C. Holten Lützhøft and S. E. Jørgensen. (1998) Occurrence, fate and effects of pharmaceutical substances in the environment – a review. *Chemosphere* 36(2):357–393.
- Hasselberg L, Westerberg S, Wassmur B, Celander M. C. (2007), "Ketoconazole, an antifungal imidazole, increases the sensitivity of rainbow trout to 17 $\alpha$ -ethynylestradiol exposure" *Aquatic Toxicology*, Volume 86, Issue 2, 31 January 2008, Pages 256–264.
- "Health at a Glance 2007" (fourth edition), OECD Indicators of the healthcare system; <http://oberon.sourceoecd.org/vl=1251620/cl=19/nw=1/rpsv/home.htm>.
- Heath R J, Rubin J R, Holland D R, Zhang E, Snow M E, Rock C O (1999). "Mechanism of triclosan inhibition of bacterial fatty acid synthesis". *J. Biol. Chem.* 274 (16): 11110–11114.
- Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi. Socialstyrelsens förslag. Stockholm: Socialstyrelsen; 2003.
- Johnson A. C, Belfroid A, DiCorcia A. (2000). "Estimating steroid oestrogen inputs into activated sludge treatment works and observations on their removal from the effluent". *The Science of The Total Environment*, Volume 256, Issues 2–3, 10 July 2000, Pages 163–173.
- Johnson A. C, Williams R. J (2004). "A model to estimate influent and effluent concentrations of estradiol, estrone, and ethinyl estradiol at sewage treatment works". *Environ. Sci. Technol.*, vol 38. pp 3649–3658
- Jones, O.A.H., N. Voulvoulis, and J.N. Lester. (2002) Aquatic environmental assesment of the top 25 English perscription pharmaceuticals. *Water Research* 36:5013–5022.
- Kidd KA, Blanchfield PJ, Mill KH, Palace VP, Evans RE, Lazorchak JM, Flick RW, (2007). "Collapse of a fish population after exposure to a synthetic estrogen". *Proceedings of the National Academy of Sciences*, 104, 8897–8901.
- Krauss, W., 1995: Mixing in the Irminger Sea and in the Iceland Basin. *Journal of Geophysical Research*, 100, 10851–10871.
- Landstinget i Uppsala län. Kartläggning av läkemedelsrester i avlopps- och dricksvatten. Provtagning vid Akademiska sjukhuset, Uppsala och Lasarettet i Enköping hösten 2005.
- Lam, Monica W, Young, Cora J, Brain, Richard A, Johnson, David J, Hanson,

- Mark A, Wilson, Christian J, Richards, Sean M, Solomon, Keith R, and Mabury, Scott A (2004) "Aquatic Persistence of Eight Pharmaceuticals in a Microcosm Study", *Environmental Toxicology and Chemistry*, Volume 23, Issue 6 (June), pp. 1431–1440.  
Press, Taylor & Francis Group.
- Landrum, PF and SW Fisher, 1999. "Influence of lipids on the bioaccumulation and trophic transfer of organic contaminants in aquatic organisms". Chapter 9 in MT Arts and BC Wainman. "Lipids in fresh water ecosystems." Springer Verlag, New York.
- Levenson A.S., Kwaan H.C., Svoboda K.M., Weiss I.M., Sakurai S., Jordan V.C. (1997) "112 Effects of estradiol on components of the plasminogen-plasmin system in MDA-MB-231 breast cancer cells stably transfected with the estrogen receptor", *Fibrinolysis and Proteolysis*, Volume 11, Supplement 3, October, Page 32
- Zong-Bin LI, CHEN Yu-Xia, ZHAO Jie-Ying, LU Jian, (2006). "Effects of Pharmacological Concentrations of Estrogens on Growth of 3AO Human Ovarian Cancer Cells", *Acta Genetica Sinica*, Volume 33, Issue 9, September 2006, Pages 782–792
- Lindberg, Richard, (2006), "Determination of Antibiotics in the Swedish Environment with Emphasis on Sewage Treatment Plants", Thesis, ISBN 91-7264-045-6.
- Loli, Paola; Maria Elisa Berselli and Mariantonella Tagliaferri (1986). "Use of ketoconazole in the treatment of Cushing's syndrome". *Journal of Clinical Endocrinology & Metabolism* 63 (6): 1365–71
- Läkemedel på sjukhem – en uppföljning av kvaliteten. Stockholm: Socialstyrelsen; 1999. Art nr 1999-37-002.
- McBain A J, Bartolo R G, Catrenich C E, et al. (2003). "Exposure of sink drain microcosms to triclosan: population dynamics and antimicrobial susceptibility". *Appl. Environ. Microbiol.* 69 (9): 5433–5442.
- "Medicines Consumption in the Nordic Countries 1999–2003", Nordic Medico Statistical Committee (NOMECO) 2004 Islands Brygge 67, DK-2300 Copenhagen S, ISBN 87–89702–52–2.
- MedlinePlus Medical Encyclopedia: Tinea versicolor  
<http://www.nlm.nih.gov/medlineplus/ency/article/001465.htm#Treatment>
- "Miljöpåverkan från läkemedel samt kosmetiska och hygieniska produkter", Rapport från Läkemedels verket, Augusti 2004
- Miller Virginia M, Jayachandran Muthuvel, Heit John A., Owen Whyte G (2006)  
"Estrogen therapy and thrombotic risk", *Pharmacology & Therapeutics*, Volume 111, Issue 3, September, Pages 792–807
- OECD Health Data 2008: Statistics and Indicators for 30 Countries, ISSN 1683–6243, [http://www.oecd.org/document/30/0,3343,en\\_2649\\_34631\\_12968734\\_1\\_1\\_1\\_37407,00.html](http://www.oecd.org/document/30/0,3343,en_2649_34631_12968734_1_1_1_37407,00.html)
- Oriba, H A (HA); Lo, J S (JS); Bergfeld, W F (WF); "Disseminated cutaneous fungal infection and AIDS. Cleveland Clinic journal of medicine. 1990 Mar-Apr; vol 57 (issue 2) : pp 189–91.
- Ortonne, J P; Lacour, J P; Vitetta, A; Le Fichoux, Y; (1992), "Comparative study of ketoconazole 2% foaming gel and betamethasone dipropionate 0.05% lotion in the treatment of seborrheic dermatitis in adults." *Dermatology* 1992-; vol 184 (issue 4) : pp 275–80.
- Orvos, D.R., Versteeg, D.J., Inauen, J. Capdevielle, M., Rothenstein, A. and Cunningham, V. 2002: Aquatic toxicity of triclosan. *Environmental Toxicology and Chemistry* 21 (7), 1338–1349.
- Reynaud, T.H., A.J. Weaver, and R.J. Greatbatch, 1995: Summer mean circulation in the northwestern Atlantic Ocean. *Journal of Geophysical Research*, 100, 779–816.
- Roberts P.H., and Thomas K.V. (2006). "The occurrence of selected pharmaceuticals in wastewater effluent and surface waters by the lower Tyne catchment". *Science of the total Environment*, vol 356, pp 143–153.
- Rule, K.L., Ebbett, V.R., Vikesland, P.J. (2005). Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. *Environ. Sci. Technol.*, 39(9), 3176–3185.
- Savin, R C; Horwitz, S N; (1986), "Double-blind comparison of 2% ketoconazole cream and placebo in the treatment of tinea versicolor." *Journal of the American Academy of Dermatology*, 1986-Sep; vol 15 (issue 3) : pp 500-3.
- Sebastine, I., Wakeman, R., 2003. Consumption and environmental hazards of

- pharmaceutical substances in the UK. *Process Safety and Environmental Protection*. 81, 229–235.
- Schwaiger J et al., *Aquatic Toxicology*, Volume 68, Issue 2, 10 June 2004, Pages 141–150.
- Thomas K.V (2007). “Occurrence of selected pharmaceuticals in wastewater effluents from hospitals (Ullevål and Rikshospitalet) and VEAS wastewater treatment works”. SFT, 2007, TA-2246/2007.
- SCB, 2001a. 2001-05-31 Nr 2001:150, Sveriges befolkning 2001–2050 – Reviderad befolkningsprognos från SCB Pressmeddelande
- Suedel, B.C., Boraczek, J.A., Peddicord, R.K., Clifford, P.A. and Dillon, T.M., 1994. “Trophic transfer and biomagnification potential of contaminants in aquatic ecosystems.” *Reviews of Environmental Contamination and Toxicology* 136: 21–89.
- Ternes, T.A. (1998) Occurrence of drugs in German sewage treatment plants and rivers. *Wat Res* 32 No.11: 3245–3260.
- Thorslund M, Lennartsson C, Parker MG, Lundberg O. De allra äldstas hälsa har blivit sämre. Könsskillnaderna är stora – kvinnorna mår sämre än männen. *Läkartidningen* 2004;101:1494-9
- UN, 1998. United Nations Population Division, *World Population Prospects: The 1998 Revision*.
- UN, 2000. *Replacement Migration: Is it a Solution to Declining and Ageing Populations?* United Nations Populations Division
- Vajda, AM, Barber, LB, Gray, JL, Lopez, EM, Woodling, JD, and Norris, DO. (2008), “Reproductive disruption in fish downstream of an estrogenic wastewater effluent.” *Environmental Science & Technology* (published on-line March 25, 2008).
- Woldegiorgis Andreas, Green Jeanette, Remberger Mikael, Kaj Lennart, Brorström-Lundén Eva, Dye Christian, Schlabach Martin. (2007). Results from the Swedish screening 2006. Subreport 4: Pharmaceuticals IVL B1751.
- Yazdankhah SP, Scheie AA, Høiby EA, et al. (2006). “Triclosan and antimicrobial resistance in bacteria: an overview”. *Microb. Drug Resist.* 12 (2): 83–90.
- Zafar A B, Butler R C, Reese D J, Gaydos L A, Mennonna P A (1995). “Use of 0.3% triclosan (Bacti-Stat) to eradicate an outbreak of methicillin-resistant *Staphylococcus aureus* in a neonatal nursery”. *American Journal of Infection Control* 23 (3): 200–208.
- Zuccato, E. et al. (2001) Environmental loads and detection of Pharmaceuticals in Italy. *Pharmaceuticals in the Environment: Sources, fate effects and risks*. K. Kummer. Springer\_Verlag, Berlin.
- Zwiener, C., T.J. Gremm, and F.H. Frimmel. (2001) Pharmaceutical residues in the aquatic environment and their significance for drinking water production. *Pharmaceuticals in the Environment: Sources, fate effects and risks*. K. Kummer. Springer\_Verlag, Berlin.

# Svensk sammanfattning

I takt med att andelen äldre i befolkningen ökar i de nordiska länderna, ökar också läkemedelsavandningen (OECD, 2008). Fler och fler läkemedel introduceras dessutom på marknaden.

Då de flesta läkemedel intas oralt och förväntas passera mag-tarmkanalen under frisättning av aktiv dos måste de med nödvändighet ha en tillräcklig kemisk stabilitet för att klara den tuffa miljön som magsäcken utgör (lågt pH-värde, aktiva enzysystem). Detta får till följd att läkemedel ofta är svårnedbrytbara eller t o m persistenta när de når den akvatiska miljön. Läkemedel anses således ofta ha låg bionedbrytningshastighet (Dughton och Ternes, 1999, Lam et al., 2004, Aga, 2007, Gibs et al., 2007). Det faktum att läkemedel ofta är stabila bidrar dessutom också till att den effektiva plasmakoncentrationen kan bibehållas en längre tid hos patienten utan att en ny dos behöver tillföras.

Läkemedel är dessutom optimerade för att ha en biologisk aktivitet som agonist eller som antagonist till någon av kroppens receptorer. Den biologiska effekten inträder vid relativt låga koncentrationer i blodplasma ( $\mu\text{g/l}$ - $\text{mg/l}$ ). Vidare så kan man konstatera att design och funktion av många viktiga biologiska receptorer konserverats under evolutionen vilket gör det troligt att ett potent humanläkemedel även kommer att inducera en biologisk effekt i vattenlevande organismer vid låga koncentrationer. Det kommer nödvändigtvis inte vara samma receptorsvar eller effekt som induceras i människor men läkemedlet kommer förmodligen ge upphov till en effekt hos den organism som exponeras (Borenstein et al., 2007, Coronado et al., 2007, Gunnarsson et al., 2008).

Då de flesta läkemedel ej har ett säsongsbärande konsumtionsmönster utan används varje dag under hela året, kan akvatiska organismer komma att tillbringa hela sitt liv konstant exponerade för en låg halt av olika läkemedel.

I denna studie har en retrospektiv analys genomförts av konsumtionsmönstret för läkemedel i de nordiska länderna under perioden 1997–2007. I studien har de läkemedelssubstanser som försäljs i de största mängderna i respektive land studerats. Antalet försålda dyngsdoser (*defined daily doses*, DDD) har räknats om till en mängd aktiv substans (i kg). På basis av antalet kg av läkemedlet som försålts har en förväntad koncentration i ytvatten beräknats (*predicted environmental concentration*, PEC, i  $\mu\text{g/l}$ ). Hur PEC-halterna varierar över tiden kan vara en god indikation på vilka läkemedel som eventuellt bör vara föremål för mer riktad miljöövervakning.

Vidare har de läkemedel som uppvisat kombinationen hög försäljning och låg effektkoncentration för akvatiska arter (PEC/PNEC-kvot, miljör-

risk) plockats ut för vidare analys. Hur miljörisken, i termer av PEC/PNEC, varierar över tiden kan ge mycket god information om hur-vida akvatiska arter riskerar att påverkas.

Den mest slående slutsatsen ifrån studien är att konsumtionsmönstret av humanläkemedel mellan de olika nordiska länderna är mycket snarlik. Listorna med "topp-30"-läkemedel ("topp-30 PEC-listan) respektive "topp-30" PEC/PNEC-listan är i stort sett densamma i alla nordiska länder. Detta är en viktig slutsats då detta likartade mönster är ett viktigt argument för att fortsatt nordisk samarbete kring frågeställningar kring läkemedlens miljöpåverkan; handlingsplaner, regulatoriska frågor, informations till allmänheten, samt fortsatt forskning.

Det finns goda skäl att i framtiden beakta rapportens olika PEC/PNEC-listor. Många av de läkemedel som toppar respektive lands PEC/PNEC-lista har ännu ej förekommit som målsubstans i nationella screeningundersökningar.

Bortsett ifrån Ketokonazol (som försäljs och används i stora mängder i framförallt Danmark och Sverige) är de läkemedel som dyker upp på miljörisklistan (PEC/PNEC-listan) i stort sett de som man kunde förutsäga skulle hamna där; könshormonerna, diklofenak, paracetamol och sertralin.

Den i rapporten föreslagna metodiken kring "Ackumulerad miljörisk", som i förekommande fall även försöker ta i anspråk rikskerna med att halterna av vissa läkemedel byggs upp succesivt i miljön år från år på en långsam bionedbrytning, är fortfarande i en begynnelsefas och måste självklart prövas experimentellt för att fortsättningsvis kunna utgöra ett riskbedömningsverktyg. Detta är de olika klasserna av bionedbrytningshastighet som föreslagits en aning *ad-hoc*-baserade. Dock, i ljuset av vår nuvarande kunskap om dessa ämnens nedbrytningshastighet föreligger de facto risker att halter byggs upp över tiden i vattenmiljön och konceptet med "ackumulerad miljörisk kan ses som ett *worst case* scenario som kompletterar den gängse PEC/PNEC-baserade miljöriskbedömningen.

I några fall är den "ackumulerade miljörisken" mycket hög, som till exempel i fallet med könshormonerna. PEC/PNEC-kvoter i närheten av 100 indikerar att i vissa nordiska recipientvatten där renat reningsverkstvatten ej späds så mycket som önskas, är det rimligt att anta att akvatiska arter redan nu påverkas.

I ett försök att sätta halter och miljörisker med avseende på läkemedelssubstanser i ett bredare perspektiv har en motsvarande analys gjorts av biociden triclosan. Triclosan används i flera konsumentnära produkter, främst i tandkräm och andra hygienprodukter. Användningsmönstret (i konsumenternas hem och badrum) gör det troligt att triclosan främst når miljön via avlopp och reningsverken – samma spridningsväg som kan förväntas för läkemedel. PEC/PNEC för triclosan är i de flesta nordiska länder mellan 2–10 (osäkerheten i användningsstatistik mellan länderna är oacceptabelt stor, bl a ingår ej kosmetika i de produktkategorier som inkluderats). Man kan konstatera användningen av triclosan i till exempel Sverige

nått sin peak och nu planar ut eller t o m minskar. Vidare så ger jämförelsen vid handen att många läkemedel kan vid dagens konsumtionsnivåer associeras med en högre miljörisk än den som kan beräknas för triclosan. För att jämförelsen mellan miljörisken ifrån läkemedelskonsumtion jämfört med miljörisken med avseende på användandet av triclosan skall vara helt adekvat krävs dock bättre och mer exakta data på omsättningen av triclosan i samhället. För de flesta av läkemedelssubstanserna är konsumtionen känd ner till gramnivå emedan osäkerheten i skattningen av triclosananvändandet är i hundratals kilo (alternativt ton).

Slutligen illustreras konceptet med en klass-specifik miljörisk för två fall; protonpumpsinhibitorer (PPIs) och serotoninåterupptagsinhibitorer (SSRIs). Då läkemedel i dessa terapeutiska klasser verkar på specifika receptorer är det rimligt att den samlade miljöriskbedömningen görs på basis av hela ämnesklassens ekotoxikologiska tryck.



# Appendix

**Table on the “*lack of data*” for persistence classification  
(retrieved from [www.fass.se](http://www.fass.se), 20090511).**

Name	ATC-code	No data on persistence	Ambiguities on fass.se in the persistence data set
Digoxin	C01AA05	X	
Isosorbidmononitrate	C01DA14	X	
Bendroflumethiazide	C03AB01	X	
Amiloride	C03EA01	X	
Atenolol	C07AB03	X	
Desogestrel	G03AC09/ G03AB05	X	
Estriol	G03CA04	X	
Flunitrazepam	N05CD03	X	
Zopiklon	N05CF01	X	
Propiomazine	N05CM06	X	
Citalopram/ Escitalopram	N06AB04/ N06AB10	X	
Oxymethazoline	R01AA05	X	
Chlorhexidine	D08AC02/ A01AB03	X	
Gestodene	G03AA10	X	
Prednisole	C05AA04/ S01BA04	X	
Levothyroxine	H03AA01	X	
Diazepam	N05BA01	X	
Alprazolam	N05BA12	X	
Triazolam	N05CD05	X	
Prometazine	R06AD02	X	
Norethisterone	G03AB04/ G03FA01	X	
Ethinylestradiol	G03AA11 etc.	X	One company claims a “3% biodegradation in 28 days,” accd. to US FDA TAD 3.11,”
Pantoprazole	A02BC02	X	
Isosorbid dinitrate	C01DA08	X	
Nifedipine	C08CA05	X	
Medroxyprogesterone	G03AC06	X	
Oxazepam	N05BA04	X	
Temazepam	N05CD07	X	
Cetirizine	R06AE07	X	
Lercanidipine	C09BB02	X	
Drospirenone	G03AA12	X	
Doxazocine	C02CA04	X	
Clotrimazole	G01AF02	X	
Indometacine	M01AB01	X	
Piroxicam	M01AC01	X	
Nabumetone	M01AX01	X	
Ketoprofen	M02AA10/ M01AE03	X	
Carisoprodol	M03BA02	X	
Probenecid	M04AB01	X	
Lynestrenol	G03DC03	X	
Tibolon	G03CX01	X	
Dienogest	G03FA15	X	
Clomifen	G03GB02	X	
Norelgestromin	G03AA13	X	
Emepromium	G04BD01	X	
Triamterene	C03DB02	X	
Bisacodyl	A06AB02	X	
Tramadol	N02AX02	X	

Name	ATC-code	No data on persistence	Ambiguities on fass.se in the persistence data set
Norgestimate	G03AA11	X	
Ramipril	C09AA05		Could be classified also as "inherently biodegradable"
Losartan	C09CA01		Could be classified also as "inherently biodegradable"
Sertraline	N06AB06		Could be classified also as "inherently biodegradable"
Zolpidem	N05CF02		Could be classified also as "inherently biodegradable"
Naproxen	G02CC02		Could be classified also as "inherently biodegradable"
Diclofenac	M01AE02, M02AA12		
	M01AB05, M02AA15, S01BC03		Could be classified also as "inherently biodegradable"
Simvastatin	C10AA01		The active drug (Simvastatin hydroxy acid ) Could be classified also as "inherently biodegradable"
Paracetamol	N02BE01		Could be classified also as "inherently biodegradable"