Svenskt Vatten

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Waste water Treatment Pains

Pharmaceuticals in our water environment

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Forword

Waste water Treatment Pains – Pharmaceuticals in our water environment, is a report from Svenskt Vatten, the Swedish water and waste water association, within the framework of the control at source work and Revaq. Revaq is a national quality assurance system for waste water treatment plants. Revaq is managed by Svenskt Vatten. A steering group is associated with Revaq in which the Federation of Swedish farmers (LRF), and the Swedish Food Federation participates. There is also a collaboration in Revaq with the Swedish Environmental Protection Agency. In previous reports Svenskt Vatten has highlighted other problematic substances that pass into waste water treatment plants. We have published reports on cadmium, triclosan, PFAS and antibacterial silver.

Our waste water treatment plants in Sweden work hard to treat waste water. This involves huge efforts to phase out toxic and harmful substances to prevent them passing into the sewers and from there, into the nature. We call this upstream work.

Using the report Waste water Treatment Pains, we wish to focus on the problems of pharmaceutical residues in our shared Swedish waters and in our waste water systems. The water and waste water organisations are experiencing a growing problem that must be dealt with. The questions cry out for answers; the techniques are available - but progress is too slow. National and EU legislation are partly inadequate and funding issues are largely unresolved.

We see certain easy solutions, such as making pharmaceuticals that contain river basin-specific pollutants prescription-only. It should be possible to achieve quite quickly.

The report addresses several involved parties: the EU, the Swedish government, the Swedish authorities, the pharmaceutical industry, the Swedish regions, prescribing doctors, pharmacies as well as the consumers of pharmaceuticals.

Using this report, Svenskt Vatten wishes to intensify and accelerate the work dealing with river basin-specific pollutants.

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Summary

This report focuses on pharmaceutical residues in our shared Swedish waters. In this report, we show that environmentally harmful pharmaceutical residues are present in our waters – and at levels that are alarming. We also discuss what we can do about these problems. That something has to be done, and by many actors, is our starting point.

Pharmaceuticals are of enormous importance for our health and well-being. It is not possible to overstate the importance of today's pharmaceuticals for us. At the same time, some pharmaceuticals are harmful to the environment.

In this report, we focus on three types of pharmaceuticals included in the 2015 Swedish National Pharmaceutical Strategy (NLS) list of pharmaceuticals that should be monitored in the environment: hormone preparations, antibiotics and analgesics. A few years ago, the Swedish Agency for Marine and Water Management decided to classify four of these as river basin-specific pollutants (RBSP): antibiotics (ciprofloxacin), hormone preparations (estradiol, ethinylestradiol), and analgesic/anti-inflammatory preparations (diclofenac[1]). These pharmaceuticals each give different types of water environmental problems. It is essential that we minimise the consequences of pharmaceutical residue dispersal in our shared waters.

Conclusions of the report:

- Figures from VISS, VattenInformationSystem Sverige, compiled by Svenskt Vatten, show that in recent years, the levels of diclofenac measured in Swedish lakes, streams and coastlines, have exceeded the limits for good ecology in 18 locations.
- There is a risk that the limit for diclofenac will be exceeded in an additional 109 Swedish lakes, streams or coastal waters. For beta-estradiol and alpha-estradiol, the corresponding number of affected watercourses is 159 and 40, respectively.
- One tube of diclofenac gel is sufficient to exceed the limit for diclofenac in a volume of coastal water equivalent to 60 x 25-metre basins for a smaller tube, and an immense 232 x 25-metre basins for a larger tube.
- According to a survey by Svenskt Vatten, 10 of 12 representatives from the regional pharmaceutical committees believe that all pharmaceuticals containing diclofenac should be prescription-only.
- The investment costs for advanced pharmaceutical waste water treatment at the Swedish waste water treatment plants is calculated at SEK 6 to 10 billion to upgrade 50–100 waste water treatment plants. This means that the cost of sewage treatment could more than double. In some municipalities, the water and waste water tariffs could amount to more than SEK 10,000–15,000 per family and year. For some groups in society, the water and waste water tariffs could be higher than the UN recommendation[2] that the water and waste water rate should be a maximum of five percent of disposable income. It is therefore necessary to introduce the extended producers responsibility (EPR) to assist the financing of advanced treatment in waste water treatment plants.

1 Diclofenac is sold under brand names such as Voltaren, Eeze, Eezeneo, Diclofenac Zentiva, Diclofenac Orifarm, Diclofenac T ratiopharm, Diclofenac Puren, and Diclofenac ABECE

2 https://www.un.org/waterforlifedecade/pdf/human_right_to_water_and_sanitation_media_brief.pdf)

Some of Svenskt Vatten's demands and proposals for measures:

- The EU should introduce extended producer responsibility (EPR) in order to regulate for the producers of pharmaceuticals to finance the treatment of pharmaceutical residues in municipal waste water treatment plants.
- Sweden will work to ensure that the EU makes it possible for Member States to decide that environmentally hazardous pharmaceuticals must only be sold with a prescription.
- Doctors should, where medically possible and safe for the patient, refrain from prescribing medicinal products that are considered by the Swedish Maritime and Water Administration to be river basin-specific pollutants, RBSP: estradiol, ethinylestradiol, ciprofloxacin and diclofenac.
- The pharmaceutical industry should review the FASS model for assessing environmental risk so that there is coherence with the substances classified by the Swedish Agency for Marine and Water Management as river basin-specific pollutants. It is not feasible to have a model that concludes, for example, that the environmental risk of diclofenac is 'negligible'.
- The Swedish Pharmacy Association should work to introduce a system so that over-the-counter pharmaceuticals can be eco-labelled.
- The water and waste water organisations must continue to monitor developments and, in dialogue with regulatory authorities, review the need to invest in advanced pharmaceutical treatment at waste water treatment plants.

The easiest way to reduce the dispersal of environmentally harmful pharmaceutical residues is to stop using the pharmaceuticals. That is neither possible nor desired. Patient safety and the medical benefits must be the top priority. Sometimes, however, adequate alternative treatments are available.

In regard to antibiotics, it is a stated objective of the Swedish authorities to reduce all unnecessary use. Objective and transparent information on the wise use of pharmaceuticals as well as their environmental impact is therefore necessary.

Where wiser pharmaceutical use, such as a decrease in the use of diclofenac, is insufficient to deal with the pharmaceutical residues, it will be necessary as a complementary measure to upgrade a number of the treatment plants. The cost of this expansion, an investment of SEK 6 to 10 billion - and the greatly increased (30 to 200%) operating costs - are the breaking points. It is necessary to introduce some form of extended producer responsibility – those who contribute to harming the water environment must contribute to the cost of minimising damage in our shared waters. In brief, the pharmaceutical manufacturers must pay their share for the treatment of pharmaceutical residues in municipal treatment plants, where this is necessary. This report therefore calls for examination of the question of producer responsibility for pharmaceuticals with a high negative environmental impact. Our politicians – both in Sweden and the EU – must act on this issue now.

Svenskt Vatten's demands and proposals for measures

We cannot turn a blind eye to the problem of the environmental impact of pharmaceuticals. We must adopt measures to ensure the good quality of our waters. Some measures can be implemented upstream. These are measures which, through prevention, aim to reduce or completely stop the dispersal of substances that harm the environment and our waters. Other measures are implemented downstream. These are measures that are implemented in the treatment plants. In regard to pharmaceuticals, multi-stage measures are needed nationally and internationally, from production through distribution and licensing processes to procurement, prescription and use.

In 2019, the OECD published the report 'Pharmaceutical Residues in Freshwater – Hazards and Policy Responses'. In the report, the OECD takes a broad approach to the issue and proposes comprehensive measures at policy level. Examples of recommended OECD actions are[3]:

OECD recommendations on use-orientated approaches. Pharmaceutical life cycle stages: prescription and use:
- Reduce self-prescription of pharmaceuticals with high-risk and illegal sales of pharmaceuticals

OECD recommendations on source-directed approaches. Pharmaceutical life cycle stages: design, marketing authorisation, manufacturing, post-authorisation:
- Develop clear and shared environmental criteria (and performance indicators) for sustainable 'green' procurement of pharmaceuticals.
- Consider expansion of the regulatory framework for good manufacturing practice to include mandatory environmental criteria

OECD recommendations on end-of-pipe measures. Pharmaceutical life cycle stages: collection and disposal, and wastewater treatment and reuse
- End-of-pipe measures should only be used in complementary to source-directed and use-orientated measures. An over-emphasis on upgrading wastewater treatment plant (WWTP) infrastructure is not a sustainable, optimal use of limited resources
- Ensure appropriate collection and disposal of waste pharmaceuticals. Educate and engage with health professionals, veterinarians, consumers and farmers to raise awareness about inappropriate disposal of unused medications. Consider extended producer responsibility schemes to recover costs.

3 https://www.oecd.org/environment/resources/pharmaceutical-residues-in-freshwater-policy-highlights.pdf

Svenskt Vatten largely shares the OECD view on which measures are needed. Svenskt Vatten has the following demands and proposals for measures as follows:

The European Union

- The EU should implement extended producer responsibility (EPR) to enable funding of pharmaceutical residue treatment by municipal waste water treatment plants. The EU should urgently determine how such producer responsibility can be designed for the internal EU market. Current EU legislation already incorporates the possibility to introduce producer responsibility. Sweden should take the initiative and act as a driving force for its implementation.
- The EU should impose environmental requirements for pharmaceuticals. For example, the licensing of new medicinal products should stipulate environmental requirements for production. Sweden should act as a trailblazer and stipulate not only environmental requirements for production but also for the supplier chain, for public procurement and for prescribing pharmaceuticals in healthcare.
- The EU should require origin marking on pharmaceuticals. An origin label would state the country and factory in which a pharmaceutical is manufactured. This transparency is necessary if we are to be able to review and assess the producer's environmental impact.
- The pharmaceutical industry today complies with good manufacturing practice, GMP, whereby pharmaceutical manufacturers commit to comply with a number of standards. This should be expanded by obligatory environment and transparency requirements. This would mean that in the future, to obtain marketing authorisation for a product throughout the EU, an importer would have to ensure that any third country manufacturer complies with the GMP requirements.
- The EU should make it possible for Member States to decide that environmentally hazardous pharmaceuticals are not to be sold without a prescription.

Sweden

The government should examine the possibility of introducing mandatory eco-marking of pharmaceuticals. In the future, marking should be taken into consideration at authorisation of medicinal products.

The government should instruct the Dental and Pharmaceutical Benefits Agency (TLV) to consider not solely the price, but also the environmental impact of a pharmaceutical during production and use, when deciding which pharmaceuticals should be included in the pharmaceutical benefit.

Sweden should work to ensure that the EU makes it possible for Member States to decide that environmentally hazardous pharmaceuticals are not to be sold without a prescription.

The regions

- The regions in Sweden should increase knowledge on the environmental impact of pharmaceuticals, in particular for prescribers. To an even greater extent than today, the regions should encourage prescribing doctors to take into account environmental considerations when prescribing and recommending pharmaceuticals.
- Doctors should, whenever possible, refrain from prescribing pharmaceuticals containing river basin-specific pollutants, RBSP i.e. the hormone preparations estradiol and ethinylestradiol, the antibiotic ciprofloxacin, and diclofenac.
- Vårdguiden (The Care Guide) should provide information on the environmental risks associated with individual pharmaceuticals.

Education

- The education of doctors, pharmacists and nurses should include the environmental impact of pharmaceuticals. The education should highlight how each profession can take into consideration the environmental risks associated with pharmaceuticals.

Pharmaceutical industry

- The pharmaceutical industry should review the FASS model for assessing environmental risk so that there is coherence with the substances classified by the Swedish Agency for Marine and Water Management as river basin-specific pollutants. It is not feasible to have a model that concludes, for example, that the environmental risk of diclofenac is 'negligible'.
- Individual pharmaceutical companies must make data on environmental risks more transparent.

The Pharmacy Association

- The Pharmacy Association should work to introduce a system so that over-the-counter pharmaceuticals can be eco-marked. In a future next step, it should be possible to eco-label all pharmaceuticals. The eco-mark should inform prescribing physicians, pharmacists and consumers about the environmental impact of a preparation. The medical benefit will always take priority, but where medically equivalent preparations are available, doctors, pharmacists and consumers can choose pharmaceuticals that have less impact on the environment. This would generate incentives for the industry to invest in pharmaceuticals with less environmental impact. Eco-labelling of pharmaceuticals can be based on some form of certification with external review, similar to the Nordic Ecolabel, the Swedish Society for Nature Conservation's Good Environmental Choice, or the Organic Food label.
- Pharmacies should stop selling over-the-counter pharmaceuticals that contain river basin-specific pollutants, RBSP, such as those containing diclofenac. There is no obligation to provide over-the-counter pharmaceuticals. Another option is to remove these pharmaceuticals from the shelves and only sell them at the counter; environmental information can then be provided at the point of sale.

Food retailers

- Food retailers should stop selling over-the-counter pharmaceuticals that contain river basin-specific pollutants, RBSP, such as pharmaceuticals containing diclofenac.

The water and waste water organisations

- The water and waste water organisations must continue to monitor and be involved in technical developments and, in dialogue with regulatory authorities, examine the need for advanced treatment of pharmaceuticals at waste water treatment plants.
- Sweden's water and waste water organisations are following the technological developments so that, when a need has been identified, upgrades can be implemented for advanced treatment of pharmaceuticals. The costs of such upgrades cannot be borne solely by the water and waste water organisations. Decisions on these investments should examine how these can be financed collectively. One element must be that the pharmaceutical producer pays a reasonable share of the financing.

The sports movement

- Sports clubs, gyms and other actors who have contact with athletes should help reduce the use of environmentally harmful pharmaceuticals, for example by disseminating information.

Consumers

- Consumers should, as far as possible, refrain from purchasing over-the-counter pharmaceuticals that have a serious impact on the environment. They should feel free to ask the pharmacy if there are other, more environmentally friendly, alternatives.

1 Introduction

This report describes how we can reduce the presence of environmentally harmful pharmaceutical residues in our shared waters. Does this mean we believe that we should stop using certain pharmaceuticals because they can have a negative impact on the water environment? The short answer is no. Pharmaceuticals are needed and the medical benefit must always take priority. However, there is a need to discuss how we can more wisely use these pharmaceuticals, which alternative treatments are available, what options are available to remove harmful residues from these pharmaceuticals when they are flushed out into the waste water, and who should bear the treatment costs in a responsible producer chain.

Pharmaceuticals are a very important part of modern society. Pharmaceuticals provide huge benefits and are important for our health and well-being. But using pharmaceuticals has side effects, undesirable effects, not only for individuals but also for society. This report pinpoints one such undesirable effect, namely the negative environmental effects of using certain pharmaceuticals.

This is an issue that has received increasing attention in recent years. Researchers have studied the presence of several active substances in watercourses, lakes and seas. It has been shown many times, particularly in the production of the active ingredients in Asia, that various pharmaceuticals are released into the environment where they are absorbed by plants and other living organisms such as mussels, worms, fish and birds.

The report focuses on three different types of pharmaceuticals that the Swedish Agency for Marine and Water Management has decided are river basin-specific pollutants (RBSP): hormone preparations (estradiol, ethinylestradiol), antibiotics (ciprofloxacin) and painkillers (diclofenac). We focus somewhat more attention on diclofenac, as it is the only one of these pharmaceuticals that is still sold without a prescription.

In the report, we publish measurements from treatment plants and watercourses which show that, in some cases, estradiol, ethinylestradiol, ciprofloxacin and diclofenac are present in concentrations that exceed their limits in lakes, watercourses and coastal water. The report describes how various measures and interventions are used – or could be used – to reduce the environmental impact of pharmaceuticals in our shared waters through wiser pharmaceutical use. It concerns reducing the use of particularly environmentally harmful pharmaceuticals. This can be achieved through a series of measures relating to the prescription of pharmaceuticals, the choice of packaging, and how unused pharmaceuticals are handled. It also concerns information, eco-labelling and origin labelling of medicinal products, as well as requirements for the authorisation processes and procurements.

We publish a survey conducted with the regions' pharmaceutical committees. In the survey, conducted in March 2020, 10 of 12 representatives for the pharmaceutical committees stated that all pharmaceuticals with diclofenac should be prescription-only.

Another question is how do we deal with pharmaceuticals in waste water treatment plants when wiser pharmaceutical use is not enough, and the limits set by the Swedish Agency for Marine and Water Management are ultimately exceeded. Today, advanced treatment techniques are available that can be used to remove unwanted pharmaceutical residues in waste water. Some technologies are more expensive than others; some solutions are highly energy and resource intensive. Overall, Svenskt Vatten estimates that the cost of investments in

treatment technology.for pharmaceuticals - for 50–100 waste water treatment plants - will amount to SEK 6 to 10 billion. The annual operating costs will come on top of this.

The report addresses the issue of these costs. It is not reasonable for consumers, municipalities or waste water treatment plants to bear these costs on their own. The pharmaceutical companies have a large responsibility. Sweden and the EU should therefore introduce extended producer responsibility, based on the principle that the producer of a harmful product has a responsibility for the consequences of the use of the product. In brief, the pharmaceutical industry must contribute to paying for the costs of the treatment of waste water pharmaceuticals.

2 Pharmaceuticals and environmental impact

2.1 A global and local issue

The global dimension of the problem of pharmaceuticals and the environment relates to awareness, regulation and control mechanisms. The EU and Sweden have regulations that, although they can be developed to be more stringent, place certain demands on the production and sales of pharmaceuticals. This shows that there is some awareness of the problem, at least in some respects. Among other things, Sweden has played an important and driving role in the fight against antibiotic resistance, and in both Sweden and the EU there have been campaigns about antibiotic resistance. The use of pharmaceuticals is increasing most outside the EU. Globally, total sales of pharmaceuticals amount to more than SEK 10,000 billion. The sales of pharmaceuticals are growing primarily in the fast-growing countries with large populations. In China, Brazil, India and Russia, the rate of increase is estimated to be more than 10% annually. For the population this is, in many respects, good news. More people can benefit from pharmaceuticals, more people can be treated, and the quality of life can be improved for many. The flip side is that in many cases the production and use of pharmaceuticals takes place without regard to risks to the environment – without regulations and control mechanisms. A very large part of the world's pharmaceutical production currently takes place in emerging countries such as China and India. In recent years, production has attracted attention because of inadequate or non-existent treatment, and high emissions at many (but not all) production facilities. This emission can, amongst others, contribute to increased antibiotic resistance.

A Swedish study[4] from 2007 identified an industrial treatment plant in India that released a wide range of pharmaceuticals at concentrations up to a million times higher than those we find in cleaned Swedish waste water. Very high concentrations of pharmaceuticals have been demonstrated in a number of other places in India, as well as in China. There are also examples of high concentrations in waste water from pharmaceutical plants in Europe and the USA.

In August 2019, Finnish Yle[5] reported that China has closed thousands of smaller-pharmaceutical plants in recent years due to alarm about widespread emission into the environment and lack of safety. China has begun work to improve the environment at its extensive pharmaceutical production and says it wants to meet its competitor, India, with higher quality instead of low prices.

A report commissioned by Apoteket Hjärtat from the RISE research institute[6] reveals water samples from a lake in an industrial area of Hyderabad, India, with continued very high concentrations of pharmaceutical residues. The report concludes that emissions from the production of pharmaceuticals are a problem which must be addressed, and that the industry itself has a responsibility to contribute.

Sweden currently uses around 1,200 active pharmaceutical substances, which corresponds to a total of about 10,000 different pharmaceuticals for both animals and humans. The vast majority have no lasting impact on the environment. However, some pharmaceuticals cause problems in the environment – not least in our shared waters. If we are to address the problems, action is needed at several levels – globally, in each country, and locally, in each municipality.

4 https://www.researchgate.net/publication/6134174_Effluent_From_Drug_Manufactures_Contains_Extremely_High_Levels_of_Pharmaceuticals

5 https://svenska.yle.fi/artikel/2019/08/16/okad-miljomedvetenhet-i-kina-leder-till-medicinbrist-i-europa

6 https://www.apotekhjartat.se/om-oss/pressrum/pressmeddelanden/atta-av-tio-vill-ha-ratt-till-informa- tion-om-hur-lakemedel-paverkar-miljon/

2.2 Environmental impact in several areas

The water environment can be affected not only in connection with production but also after use because the pharmaceutical residues in waste water pass through the waste water treatment plant into the water and the environment. In Sweden, the severest impact on the water environment comes from pharmaceutical residues in waste water that passes through treatment plants.

2.3 Environmental risk and hazard

When discussing pharmaceuticals, distinction should be made between environmental hazard/harm and environmental risk. Environmental hazard relates to the properties of a pharmaceutical, such as its toxicity and ability to withstand degradation in nature. Environmental risk also takes into account how much of the pharmaceutical passes into the natural environment, i.e. the degree to which organisms are exposed[7]. This report does not contain calculations by Svenskt Vatten of the environmental risk or environmental harm. However, we are interested in how much of the pharmaceuticals pass into the water. We present several measurements on the occurrence of pharmaceutical substances in treatment plants and in lakes, watercourses, and the sea.

2.4 Limitations

The OECD provides examples of 11 groups of pharmaceuticals that in laboratory tests have been shown to have measurable effects on aquatic organisms[8]. The list includes diclofenac and antibiotics.

Table 1. Examples of measured effects of certain pharmaceutical residues on aquatic organisms in laboratory studies

Therapeutic group	Examples of Pharmaceutical	Impact and effected organisms
Analgesics	Diclofenac, Ibuprofen	Organ damage, reduced hatching success (fish) Genotoxicity, neurotoxicity and oxidative stress (mollusk) Disruption with hormones (frog)
Antibiotics	-	Reduced growth (environmental bacteria, algae and aquatic plants)
Anti-cancer	Cyclophosphamide*, Mitomycin C, Fluorouracil	Genotoxicity
Antidiabetics	Metformin	Potential endocrine-disrupting effects (fish)
Anti- convulsants	Carbamazepine, Phenytoin, valproic acid	Reproduction toxicity (invertebrates), development delay (fish)
Antifungals	Ketoconazole, Clotrimazole Triclosan	Reduced growth (algae, fish), reduced algae community growth
Antihistamines	Hydroxyzine, Fexofenadine, Diphenhydramine	Behaviour changes, growth and feeding rate (fish) Behaviour changes and reproduction toxicity (invertebrates)
Antiparasitics	Ivermectin	Growth and reduced reproduction (invertebrates)
Beta blockers	Propranolol	Reproduction behaviour (fish), reproduction toxicity (invertebrates)
Endocrine disrupting pharmaceuticals	E2, EE2, Levonorgestrel	Disruption with hormones causing reproduction toxicity (fish, frogs)
Psychiatric dugs	Fluoxetine, Sertraline, Oxazepam, Citalopram, Chlorpromazine	Behaviour changes - feeding, boldness, activity, sociality (fish) Disruption with hormones (fish) Behaviour changes - swimming and cryptic (invertebrates) Reproduction toxicity and disruption with hormones (invertebrates)

7 https://www.lif.se/grundfakta/lakemedel-och-miljo/

8 https://www.oecd.org/environment/resources/pharmaceutical-residues-in-freshwater-policy-highlights.pdf

In this report, we focus on three types of pharmaceuticals that are on the Swedish National Pharmaceutical Strategy (NLS) list of pharmaceuticals that should be monitored in the environment[9]: hormone preparations, antibiotics and analgesics. Among these are four substances which, according to the Swedish Agency for Marine and Water Management, are river basin-specific pollutants, RBSP: estradiol, ethinylestradiol, ciprofloxacin and diclofenac, and therefore we focus specifically on these substances. Diclofenac is sold without a prescription and therefore receives somewhat more attention in the report.

2.5 Linguistic simplifications

In the report we use 'estradiol' and 'ethinylestradiol' instead of 17-beta-estradiol and 17-alpha-ethinylestradiol, respectively. The names of the pharmaceutical substances, estradiol and ethinylestradiol, are to be found in FASS.

2.6 Diclofenac

Diclofenac is an active substance that relieves pain and inhibits inflammation. The substance belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). The effects of diclofenac in the environment have been well publicised for many years. The 1990s saw the death of large numbers of Indian vultures, and it soon became apparent that they had eaten carrion from cattle treated with diclofenac[10]. Since then, many studies have been conducted on how diclofenac affects animals, including fish and other aquatic organisms. A number of studies show that concentrations of one microgram of diclofenac per litre of water can have effects on the gills and kidneys of fish[11]. This has attracted the attention of several regions in Sweden. For example, Region Stockholm[12] considers the acute toxicity of diclofenac for aquatic organisms to be high. Due to its impact on the water environment, the Swedish Agency for Marine and Water Management has determined that diclofenac is a river basin-specific pollutant, RBSP. One of the major problems with diclofenac is that it is resistant to degradation in the standard biological treatment processes used by waste water treatment plants[13] [14]. Therefore, the capacity of treatment plants to handle diclofenac is of particular interest. About 50% of the diclofenac used in Sweden comes in a gel form. What is worth noting about this gel is that only 5-6% of the substance is absorbed through the skin. This means that the remainder, i.e. more than 90 percent, is rinsed off directly during a shower or bath. It will then either end up in the waste water, or directly in the sea or lake from outdoor swimming.

In the interests of the water environment, various measures have been implemented to limit the use of diclofenac. The substance is included in the Region Stockholm list of environmentally harmful pharmaceuticals[15] and is listed as not recommended in the 'Wise List'. Region Kalmar[16] recommends that use of gels (external NSAIDs) should be restricted.

9 http://web02.lv.episerverhosting.com/upload/nyheter/2015/miljoindikatorer-rapport-NLS_2015-09-07.pdf

10 https://www.nature.com/articles/nature02317

11 https://europepmc.org/article/med/28601012

12 https://www.janusinfo.se/beslutsstod/lakemedelochmiljo/databasmiljosv/diklofenak.5.30a7505616a041a0 9b065792.html

13 Swedish Medical Products Agency (2004), Environmental impact of pharmaceuticals and cosmetic and hygienic products.

14 https://www.researchgate.net/publication/7776681_Occurrence_and_fate_of_pharmaceutically_active_ compounds_in_the_environment_a_case_study_Hje_River_in_Sweden

15 https://www.sll.se/globalassets/6.-om-landstinget/hallbarhet/miljo/forteckning-over-miljobelastande-la- kemedel2.pdf

16 https://www.ltkalmar.se/Documents/Samarbetsportalen/V%C3%A5rdriktlinjer/L%C3%A4keme- del/L%C3%A-4kemedelsnytt/2018/L%C3%A4kemedelsnytt%202018-nr%204%20Milj%C3%B6aspekter%20 p%C3%A5%20diklofenak%20utv%C3%A4rtes.pdf

From 1 June 2020, diclofenac in tablet and capsule form is only available on prescription in Sweden. However, the fact that the substance is prescription-only has nothing to do with environmental risks. Rather, an increased risk of side effects has led to this decision: 'In a comprehensive study from 2018, an increased risk of atrial fibrillation, stroke, heart failure, heart attack and death due to cardiovascular disease was seen for men and women of all ages, even at lower doses of diclofenac and shorter duration of treatment'.[17] The Medical Products Agency refers to this study: Diclofenac use and cardiovascular risks: series of nationwide cohort studies[18]. Diclofenac in gel form will continue to be sold without a prescription.

2.7 Hormones

Estrogen is used for the treatment of menopausal symptoms, for example. Estradiol, which is the most common type of estrogen treatment, relieves sweating, flushing, and discomfort in the genital area. Ethinylestradiol, which is a synthetic form of estrogen, is used as a contraceptive (oral contraceptive) and for the treatment of acne.

Because of their properties in the water environment, estradiol and ethinylestradiol are classified as river basin-specific pollutants (RBSP) in accordance with the Swedish Agency for Marine and Water Management. Both substances are monitored by the EU on the Water Framework Directive Watch List. Hormones that are dispersed in water can cause problems for fish and other living organisms; for example, they can inhibit reproduction and cause other disruptions. Ethinyl estradiol is highly potent and several studies have shown that concentrations as low as one nanogram per litre of water have effects on the sex and fertility[19] of aquatic animals and fish19. Estradiol can result in feminisation in fish[20].

2.8 Antibiotics

It is a well-known fact that the use of antibiotics can result in antibiotic resistance. This is a major challenge for public health and healthcare. Around 700,000 people die every year around the world as a result of antibiotic resistance. This number is projected to increase to ten million people annually by 2050[21]. In the EU, some 303,000 people die each year because of resistant bacteria[22].

Due to the impact of its properties on the water environment, the Swedish Agency for Marine and Water Management has determined that the antibiotic ciprofloxacin is a river basin-specific pollutant, RBSP[23]. In this report, we therefore we focus on ciprofloxacin which is a broad-spectrum antibiotic used for severe respiratory and urinary tract infections. Even in very small concentrations in the environment, ciprofloxacin can contribute to the development of antibiotic resistance[24].

17 https://www.lakemedelsverket.se/sv/nyheter/tabletter-och-kapslar-med-diklofenak-blir-receptbelagda

18 https://www.ncbi.nlm.nih.gov/pubmed/30181258?dopt=abstract

19 https://www.ncbi.nlm.nih.gov/pubmed/15793829

20 https://www.ncbi.nlm.nih.gov/pubmed/15159526

21 https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf

22 https://lakartidningen.se/aktuellt/nyheter/2018/11/antibiotikaresistens-bakom-33-000-dodsfall-i-euro- pa-under-ett-ar/

23 https://www.havochvatten.se/download/18.67e0eb431695d8639337366a/1552573474210/2013-19-keu-2019-01-01-ersatt-av-2019-25.pdf

24 https://janusinfo.se/beslutsstod/lakemedelochmiljo/databasmiljosv/ciprofloxacin.5.30a7505616a041a09b0655d3.html

3 Laws and regulations

3.1 Regulations for pharmaceuticals

Medicinal products on the European market are controlled by a comprehensive regulatory framework aimed at ensuring quality, safety and medical efficacy. The regulatory framework is widely harmonised within the EU/EEA, in part through the Directive on Human Medicinal Products [25], the Directive on Veterinary Medicinal Products[26] and the establishment of a European Medicines Agency, the EMA.

The main task of the European Medicines Agency is to protect and promote public health and animal health by evaluating and monitoring medicinal products. Pharmaceutical companies apply to the EU Commission for a marketing authorisation. If authorisation is given, they can sell the pharmaceutical in all EU and EEA countries. The European regulatory framework for pharmaceuticals is thus based on a network of about 50 regulatory authorities from the 31 EU countries (27 EU Member States plus the UK, Iceland, Liechtenstein and Norway), the EU Commission, and the European Medicines Agency.

In Sweden, the Swedish Medical Products Agency is the regulatory and competent authority for the approval and control of pharmaceuticals. The Swedish Medical Products Agency also issues licences for production of pharmaceuticals in Sweden. Manufacturing authorisations in accordance with pharmaceutical legislation are completely separate from authorisations subject to environmental legislation.

For over-the-counter pharmaceuticals, the regulations do not take into account potential environmental risks, but rather they assess the suitability of the product for self-care within the framework of the approved target population.

Legislation does not enable the Swedish Medical Products Agency to oppose the marketing of medicinal products on the grounds of increased environmental risk. It can only provide information on the environmental risks and thereby reduce the use of a particular pharmaceutical. If, in the choice between different treatment options, the treatment effect is weighed against environmental effects, the medical benefit always takes precedence over any environmental impact. Regulatory changes could open up the possibility of introducing requirements such as inclusion of environmental considerations in the benefit/risk assessment when authorising pharmaceuticals; requirements for risk reducing measures; making environmental data available in a collective manner; and emission limitations on active substances during production.

3.2 Regulations for water and pharmaceuticals

The EU Water Framework Directive (WFD) provides a common regulatory framework that applies to all water districts in Europe. This means that the same rules apply, and that all assessments are carried out in the same way in order to ensure good water quality in European waters. Furthermore, the Directive calls for the status of all waters to be established as well as the extent to which waters are affected by humans. It has the overall objective of achieving good ecological and chemical status for all waters by 2027.

The WFD includes a list of chemical substances, the Watch List, which are to be monitored by all countries in the EU. If the substance is found at risk levels in many EU countries, the next sub-process is to decide whether to include the substance on the list of priority substances in

25 Directive 2001/83/EC of the European Parliament and of the Council establishing Community rules on medicinal products for human use

26 Directive 2001/82/EC of the European Parliament and of the Council establishing Community rules on medicinal products for veterinary use

Annex 2013/39/EU[27] of the WFD. The EU Watch List currently contains a number of pharmaceutical substances. Including ethinylestradiol (EE2), estradiol (E2) and ciprofloxacin.

The EU list of priority substances contains those substances that are considered to pose a risk to the water environment and have harmonised limits for all EU countries – the aim here is to achieve good chemical status, that is to say, none of the priority substances shall exceed these limits in watercourses, seas, or coastal areas. If these are exceeded, measures must be put in place. The prioritisation of substances in the Priority Substance Directive is based on risk and limits compiled by an EU expert group.

Due to the risk of ecotoxic concentrations in water, diclofenac has previously been monitored under EU water legislation and placed on the Watch List[28]. There is now sufficient data to assess whether diclofenac should be proposed as a priority substance. It is likely that when the EU Commission next proposes a revised priority substance directive, it will be included in the list of priority substances.

27 https://www.havochvatten.se/download/18.276e7ae81443563a7505731/1396270397464/prioterade-am- nes-direktivet-2013.pdf

28 https://circabc.europa.eu/sd/a/d88900c0-68ef-4d34-8bb1-baa9af220afd/DiclofenacEQSdossier2011.pdf

4 What are others doing? An overview

In Sweden, a number of initiatives are underway to limit the impact of pharmaceuticals on the environment. The following is an overview of some of the most important initiatives and measures undertaken by authorities and other stakeholders.

4.1 Swedish National Pharmaceutical Strategy (NLS)

In 2011, the Swedish government, the Swedish Association of Local Authorities and Regions, and a number of other actors, produced the National Pharmaceutical Strategy. The aim of this was to 'bring about a national collective effort around priority initiatives in the pharmaceutical sector'. One of the strategy's five long-term goals is a focus on achieving a minimal environmental impact[29]. The NLS working group has, among other things, produced a list of substances that should be monitored in the environment[30].The list includes the substances that are the focus of this report.

4.2 The Swedish Medical Products Agency's Knowledge Centre for Pharmaceuticals in the Environment (Läkemedelsverkets kunskapscentrum för läkemedel i miljön)

The Swedish Medical Products Agency has intensified its work both nationally and internationally to reduce environmental pollution in water. In 2018, the Knowledge Centre for Pharmaceuticals in the Environment was established, the aim of which is to increase the dissemination of knowledge and stimulate action and development, thereby contributing to Sweden's generational objectives, environmental quality objectives, milestones, and the global goals defined in the UN Agenda 2030[31].

4.3 Environmental considerations in legislation

The Swedish Medical Products Agency is working on the issue of environmental considerations in the legislation for pharmaceuticals for human use. This is a targeted milestone within the national environmental quality goals. Because the majority of the legislation is regulated at EU level, Sweden cannot have different rules to the rest of the EU in these areas, even though the legislation does on occasion leave room for additional national provisions covering additional requirements or exemptions. For example, there is some freedom to decide which pharmaceuticals, based on medical reasons, should be prescription-only. This is why Sweden cannot have stricter environmental requirements than the rest of the EU. EU pharmaceutical legislation does not provide the opportunity to impose environmental requirements on the manufacture of medicinal products.

29 http://web02.lv.episerverhosting.com/upload/nyheter/2015/miljoindikatorer-rapport-NLS_2015-09-07.pdf

30 https://www.lakemedelsverket.se/nls

31 https://www.lakemedelsverket.se/sv/miljoarbete/kunskapscentrum-for-lakemedel-i-miljon#hmainbody1

4.4 Environmental data

The Swedish Medical Products Agency has worked hard to make environmental data for pharmaceuticals accessible. One example is the sales statistics produced by the Swedish Medical Products Agency in November 2019. The statistics contained a list of 42 pharmaceutical substances considered to have a negative impact on the environment.[32]

4.5 Environmental risk assessments

The Swedish Medical Products Agency has requested and received approval to improve the environmental risk assessment (ERA) performed in connection with the application for a marketing authorisation for a medicinal product. An update has been necessary because the 2006 guideline was based on industrial chemicals. This is now being handled by a working group within the European Medicines Agency.

4.6 Limits for production

Internationally and within the EU, the Swedish Environmental Protection Agency, the Swedish Food Agency and the Swedish Chemicals Agency work together with other Swedish authorities and organisations to set emission limits for the manufacture of antibiotics and pharmaceuticals with endocrine disrupting properties, among others.

4.7 Pharmaceuticals and water

The Swedish Medical Products Agency has a special responsibility to ensure that pharmaceuticals are not dispersed to the water environment. The Agency shall work to reduce the impact of medicinal products on the water environment, in particular with regard to prioritised and river basin-specific pollutants (ethinylestradiol, estradiol, diclofenac and ciprofloxacin) that affect the conditions for compliance with environmental quality standards for water.

4.8 River basin-specific pollutants (RBSP)

Each EU country can produce its own lists and limits for river basin-specific pollutants. In Sweden, the Swedish Agency for Marine and Water Management decides which substances are to be considered river basin-specific pollutants, RBSP. These are substances that are released in significant quantities and pollute the water environment. RBSP is an environmental quality standard for assessing ecological status. More information in the section Environmentally harmful pharmaceuticals in our waters.

4.9 Environmental criteria in procurement

Sweden's regions can use environmental criteria when procuring pharmaceuticals. The Act (2007:1091)[33] even states that contracting authorities 'should take environmental consid-

32 https://www.mpa.se/sv/miljoarbete/lakemedelsverkets-miljoarbete/miljorapporter

33 https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-20071091-om-of- fentlig-upphandling_sfs-2007-1091

erations into account' if justified by the contract. Each region decides for itself the extent to which the environmental criteria are to be applied[34].

4.10 The pharmaceutical benefit

The Dental and Pharmaceutical Benefits Agency (TLV) does not currently include environmental considerations when deciding which pharmaceuticals should be included in the pharmaceutical benefit. However, TLV has previously assessed that there are no fundamental obstacles to weighting environmental impact in the calculations.

The Swedish government report (2013:23) Compensation for pharmaceutical harm and environmental considerations in the pharmaceutical benefit, concluded that there are a number of practical considerations that must be in place for this to happen: 'One prerequisite if environmental impact is to be taken into account in subsidy decisions, is access to information on the environmental impact of each pharmaceutical. This means that the environmental impact... must be quantified and relatable to the measurement of health'[35]. However, it is concluded that, under the current system, it is not possible to obtain sufficient data on environmental impacts.

4.11 National collaboration on antibiotic resistance

The Swedish Public Health Agency and the Swedish Board of Agriculture are responsible for the national collaboration on antibiotic resistance and healthcare-associated infections. The collaboration started in 2012 and today a total of 25 authorities participate. STRAMA, which was originally formed by the county councils, forms part of this collaboration. The national collaboration also has initiatives directed at the general public. The campaign Protect Antibiotics, which aims to reduce the unnecessary use of antibiotics, is one such initiative.

4.12 Investment aid for waste water treatment plants

The Swedish Environmental Protection Agency has been commissioned by the Swedish government to allocate SEK 190 million in investment aid to water treatment plants for treatment of pharmaceuticals. Preliminary studies, pilot studies, or investment projects are currently underway at 30 treatment plants in the following locations in the country: Umeå, Åre, Sundsvall, Falun, Borlänge, Tierp, Uppsala, Karlstad, Haninge, Örebro, Botkyrka, Lidköping, Visby, Gothenburg, Kungsbacka, Borås, Ullared, Växjö, Östra Göinge, Ronneby, Kristianstad, Helsingborg, Landskrona, Malmö, and Simrishamn. With the help of funding from the Swedish Environmental Protection Agency, Svenskt Vatten has started a client group to support the treatment plants. For more information[36].

4.13 Läkemedelsindustriföreningen, LIF

Läkemedelsindustriföreningen (LIF) is the trade association for the research-based pharmaceutical industry in Sweden. LIF conducts its own environmental work and cooperates on certain projects with other bodies. In 2004, LIF proposed the classification system for medicinal substances that is used on Fass.se (see below). Since 2017, LIF and IVL have

34 https://www.regeringen.se/rattsliga-dokument/statens-offentliga-utredningar/2013/04/sou-201323/

35 https://www.regeringen.se/rattsliga-dokument/statens-offentliga-utredningar/2013/04/sou-201323/

36 https://www.svensktvatten.se/vattentjanster/avlopp-och-miljo/reningsverk-och-reningsprocesser/bestal- lar-grupp-lakemedelsrester-mikroplaster-och-andra-fororeningar/

cooperated on a project aimed at better understanding where and how the pharmaceuticals impact the environment. The association states on its website 'LIF has, for many years, actively worked to increase knowledge about pharmaceuticals and their potential impact on the environment, both within the pharmaceutical industry as well as among stakeholders and the general public'[37].

On its website, LIF currently lists six measures under the heading 'How we can reduce the environmental impact of pharmaceuticals':

- In order to minimise disposal of pharmaceuticals, it could be beneficial to prescribe starter packs when new pharmaceuticals are to be tried by a patient.
- Patients should be advised that pharmaceuticals must not be disposed of in household waste or flushed down the toilet. All unused pharmaceuticals should be handed in at pharmacies.
- Packaging that contains visible residues of medicinal products must be handed in to pharmacies.
- Pharmaceutical packaging in opaque material, e.g. tubes and cans, aerosol dispensers and powder inhalers, vials and ampoules, and packages containing infusion fluids containing medicinal substances, are to be handed in to pharmacies.
- Used transdermal patches and vaginal rings are to be handed in to pharmacies.
- Empty packaging is sorted like other household waste.

4.14 Individual projects with industry

Individual pharmaceutical companies run their own environmental work and are involved in collaborations with other organisations and the research institute. One example is AstraZeneca and the World Wildlife Fund which announced in spring 2020 that they are starting a collaboration to map the company's impact on water. AstraZeneca shall, among other things, identify risks and develop recommendations for the company's long-term management of water[38].

4.15 The Swedish Medical Association

The Swedish Medical Association, in collaboration with the Swedish Association of Doctors for the Environment and the Swedish Association of General Practice have developed a set of concrete tips on what doctors can do to reduce the impact on the environment and the climate.[39]

37 https://www.lif.se/fragor-vi-arbetar-med/ovriga/lakemedel-och-miljo/

38 http://www.pharma-industry.se/astrazeneca-och-wwf-i-samarbete-for-mer-hallbar-vattenforvaltning/

39 https://slf.se/app/uploads/2020/05/lakemedel-och-miljo-2020.pdf

5 Information on pharmaceuticals and the environment

Clear and accurate information is a prerequisite if consumers, pharmacists, health professionals, regions, authorities and politicians are to make informed decisions. For example, to be able to minimise the impact on the environment. It is therefore absolutely essential that information on the possible environmental impact of medicinal products is available. In this section, we review the main channels for information on environmental impacts.

5.1 Information from the pharmacies

Apoteket Hjärtat launched its own initiative in 2016 and began to label over-the-counter pharmaceuticals with a sustainability label. This model has now been handed over to the entire pharmacy industry and, in 2020, the Swedish Pharmacy Association has a project ongoing to produce a common guide for all pharmacies in the country.

In regard to diclofenac, the members of the Swedish Pharmacy Association have all agreed to inform consumers that diclofenac has a negative environmental impact. This has been ongoing since 3 October 2018. The information is provided on shelf edges in stores, for example. It may say: Diclofenac adversely affects the nature, use with consideration. The agreement applies to both in-store and e-commerce sales. A press release states: There is a greater risk of negative environmental impact with diclofenac compared to other over-the-counter analgesics such as naproxen, ibuprofen and paracetamol.[40]

Cecilia de Pedro, Head of Sustainability at Apoteket Hjärtat, points out in an interview with The Pharmaceutical World that there are currently no environmental requirements for pharmaceuticals, while at the same time their customers demand information about the environmental impact of pharmaceuticals. 'Customers ask questions, and we can no longer just provide the cheapest, but we want environmental requirements imposed on the prescription range in the future'[41]. Cecilia de Pedro told Svenskt Vatten 'We know from studies we have conducted that customers want to know more about how pharmaceuticals are produced and how they affect the environment'.

Apoteket Hjärtat and the Pharmacy Association are pushing the issue of sustainability labelling and have developed a system that was released in February 2021. In a poll from Novus[42], 80 percent of respondents said they should have the information to be able to know how prescription drugs affect the environment. Sixty-one percent wanted to see stricter environmental requirements when procuring pharmaceuticals. In the 18—29 age group, the figures were even higher.

Information on pharmacies' websites

We reviewed the pharmacies' websites to see whether they provide information for consumers about diclofenac and environmental impact. Six of seven websites state: Diclofenac negatively affects the nature, use with consideration. The only pharmacy that does not provide this information on its website is the state-owned Apoteket.se, which only refers to fass.se. Read more about Fass below.

40 https://janusinfo.se/nyheter/nyheter/2018/miljovarningfordiklofenakpaapoteken.5.4553c- 8616621d6afc55099c.html

41 https://www.lakemedelsvarlden.se/ny-rapport-stora-utslapp-vid-indisk-lakemedelstillverkning/

42 https://www.apotekhjartat.se/om-oss/pressrum/pressmeddelanden/atta-av-tio-vill-ha-ratt-till-informa- tion-om-hur-lakemedel-paverkar-miljon/

Pharmacy environmental information for consumers about diclofenac on websites

Apotea.se	Diclofenac adversely affects the nature, use with consideration.
Apotekhjartat.se	Diclofenac adversely affects the nature, use with consideration.
Kronansapotek.se	Diclofenac adversely affects the nature, use with consideration.
Meds.se	Diclofenac adversely affects the nature, use with consideration.
Apoteksgruppen.se	Diclofenac adversely affects the nature, use with consideration.
Lloydsapotek.se	Diclofenac adversely affects the nature, use with consideration.
Apoteket.se	No environmental information on diclofenac. Refers to fass.se

Considerations by pharmacies

On the whole, pharmacies take a greater responsibility for the environment and sustainability. At the same time, there is a conflict of interest between the economy and the desire to contribute to a good environment, because the products that are not prescription-only are those that generate the pharmacies' profit margin. Pharmaceutical companies can today pay for the exposure and marketing of over-the-counter goods in pharmacies.

Voluntary sale of over-the-counter pharmaceuticals

Pharmacies are under no obligation to sell over-the-counter pharmaceuticals. The obligation to provide pharmaceuticals applies only to prescription products. In other words, an individual pharmacy can opt out of selling a pharmaceutical, for example because of environmental considerations. Or they can remove these pharmaceuticals from store shelves and only sell them over the counter where environmental information can be provided at the point of sale.

5.2 Information from the Regions

The country's regions compile information on the environmental impact of pharmaceuticals for healthcare providers. Each region's Committee on Medicinal Products, LOK, which are responsible for promoting the reliable and rational use of medicinal products in the region, recommend to varying degrees that the health services take into account the environmental perspective when using and prescribing individual pharmaceuticals.

In Stockholm, the information is compiled on Janusinfo.se and a substance's environmental hazard or environmental risk is classified. The hazard to the environment is assessed on a scale from 09, where 9 indicates higher environmentally hazardous properties. Region Stockholm has produced a list of environmentally harmful pharmaceuticals, with proposals for measures. All substances covered in this report are included on the list of pharmaceuticals deemed to be an environmental burden.

In several other regions, the pharmaceutical committees make similar recommendations for healthcare, and specifically mention diclofenac as a preparation that imposes a burden on the environment. In Region Kalmar, the Pharmaceutical Committee writes[43]: When diclofenac is applied externally, only a small amount is taken up systemically. This is an advantage given the risk of cardiovascular and gastrointestinal side effects. The bioavailability of diclofenac in gel applied to the skin is 56%. If you apply the highest recommended dose of any of the diclofenac gels sold in Sweden, the total daily dose of diclofenac on the skin will be approximately 185 mg. Taking into consideration that 90-95% of this will not to be absorbed, but washed down the drain when showering or bathing. Some may get caught on clothes and then pass with the washing water out into the drain.

43 https://www.ltkalmar.se/Documents/Samarbetsportalen/V%C3%A5rdriktlinjer/L%C3%A4keme- del/L%C3%A-4kemedelsnytt/2018/L%C3%A4kemedelsnytt%202018-nr%204%20Milj%C3%B6aspekter%20 p%C3%A5%20diklofenak%20utv%C3%A4rtes.pdf

5.3 FASS (environmental classification)

Fass is the pharmaceutical industry's source of information on pharmaceuticals for both the general public and healthcare professionals. Behind Fass is the Läkemedelsindustriföreningen (LIF) Service AB. About 210 companies contribute to the content of Fass.

In addition to information on the use of pharmaceuticals, adverse reactions, etc., Fass also provides information on individual pharmaceuticals and the environmental effects of medicinal substances. This environmental information is based on the pharmaceutical industry's environmental classification system. The system is voluntary and was developed by LIF in collaboration with Apoteket AB, the Swedish Medical Products Agency, Stockholm County Council and the Swedish Association of Local Authorities and Regions. The environmental classification is allocated after the pharmaceutical company compiles information on which it conducts an environmental risk assessment of the pharmaceutical substances. Before the information is published, it must be reviewed by an external reviewer, IVL (Swedish Environmental Research Institute), who checks that the assessment has been correctly performed and complies with the requirements of the model.

How Fass describes its environmental classification: In Fass you will find information about how much impact a pharmaceutical has on the environment. Here you will find out, among other things, whether the pharmaceutical has a high or low risk for the environment. The environmental classifications are based on how harmful the substances have been shown to be to organisms, using experimental tests. The classification is based on each pharmaceutical company producing information and conducting an environmental risk assessment for its pharmaceutical substances. The classification is checked before publication by IVL, Swedish Environmental Research Institute.

From LIF's perspective, the purpose of environmental classification of medicinal products is to provide environmental information that could be used to select pharmaceutical treatment and prescriptions that reduce environmental impact. LIF also believes that by publishing data on Fass.se, they reach out to many healthcare professionals.

Environmental information in Fass

Fass includes the following environmental information on diclofenac, ciprofloxacin and estradiol:

Diclofenac	Environmental risk: The use of diclofenac has been assessed as having a negligible risk of environmental impact. Degradation: Diclofenac decomposes slowly in the environment. Bioaccumulation: Diclofenac has a low potential to bioaccumulate.
Ciprofloxacin	Environmental risk: The use of ciproflaxin has been assessed as having a high risk of environmental impact. Degradation: Ciprofloxacin is potentially persistent. Bioaccumulation: Ciprofloxacin has a low potential to bioaccumulate.
Estradiol	Environmental risk: The use of estradiol has been assessed as having a moderate risk of environmental impact. Degradation: Estradiol breaks down slowly in the environment. Bioaccumulation: Estradiol has a high potential to bioaccumulate.

Source: fass.se

Questions have been asked about the environmental information on Fass.se. One comment is that it is somewhat contradictory that the same substance can have different environmental classifications in Fass depending on which pharmaceutical company has submitted the data.[44] That is because the companies' data can differ which, for substances close to a limit, can result in differing environmental classifications. Ethinylestradiol, estradiol and diclofenac have been cited as examples of this.

44 https://www.ivl.se/download/18.3016a17415acdd0b1f416/1489594583926/B2274.pdf

The Chairman of the LIF Environment Committee has responded to this criticism thus: 'Users of the system must be quite well-informed. It cannot be left to the individual doctor to understand all aspects. We have concluded that the target group for the system is the county councils' pharmaceutical committees and their expert groups rather than individual doctors'[45].

There have also been discussions[46] about the difference between the environmental information on Fass.se and, for example, Janusinfo.se, which includes more far-reaching environmental risk assessments than Fass.se. According to Fass, the environmental risk of diclofenac is considered to be negligible, which has raised questions.

This is how IVL writes in an email to Svenskt Vatten: The environmental risk assessments at Fass.se are based on the conditions that exist in Sweden and is a weighted, overall assessment of environmental hazard and environmental risk that also takes into account the amount of sold substance. According to the criteria set out in the Fass Review Guide, which are based on EMA guidelines, diclofenac meets the requirements for the classification 'negligible risk' based on the data they have submitted. Since it can appear slightly contradictory, we as Fass reviewers at IVL have often discussed this particular substance, and the pharmaceutical companies have agreed to add the supplementary text to the environmental document on the conditions of the vultures in India and Pakistan:

> *'Vulture (old world) populations in India and Pakistan were exposed to comparatively high concentrations of diclofenac via the very exceptional pathway of extensive diclofenac use in cattle. The pathway: veterinary use in cattle - leaving of dead cattle for vultures to feed upon (for cultural reasons) and subsequent secondary poisoning leading to acute toxic effects in vultures are unlikely to be applicable to the situation in Sweden. Based on the low bioconcentration factor found in our study (Harlan Laboratories Study D24068) on bioconcentration in fish, similar effects are not expected in fish eating birds, as the bioaccumulation via the pathway "patients use as human pharmaceutical - excretion/wash-off to sewer systems - intake into surface waters - bioconcentration in fish - accumulation in fish-eating birds" is not expected to be significant and consequently not expected to lead to acute toxic effects in birds.'*

Criticism of the documentation of medicinal products

Since 2006, environmental effects of pharmaceuticals have to be documented by pharmaceutical companies in order to be approved for the European market. Companies must document effects on the environment during production and use. The documentation that forms the basis for the industry's environmental classification is publicly available on Fass. There is a greater lack of knowledge on the environmental effects of older pharmaceuticals, approved before 2006. The same applies to medicinal products that are no longer patented.

One criticism of the companies' classification is that there is uncertainty in the risk assessment. This is summarised in The Swedish Medical Products Book[47], which is published by the Swedish Medical Products Agency:

45 https://www.dagensmedicin.se/artiklar/2010/11/10/kritik-mot-miljosystem/

46 https://www.ivl.se/download/18.3016a17415acdd0b1f416/1489594583926/B2274.pdf

47 https://lakemedelsboken.se/kapitel/lakemedelsanvandning/lakemedel_i_miljon.html

Although a large number of products have been given an environmental classification, there is still a high level of uncertainty in the risk assessment, as the tests that form the basis for the rating unfortunately often lack identification of possible effects. In particular, for the vast majority of pharmaceuticals, long-term studies on fish are lacking. Extrapolations from toxicity tests on waste water and algae and fish provide an inadequate basis, even if a safety factor is applied. Another shortcoming is revealed when it can be found that different products with the same substances have different classifications, probably partly because it is the companies themselves that report the data. With today's medical records system, it is difficult for the prescriber to quickly get a good overview of the environmental profile of alternative pharmaceuticals when writing the prescription. The presence of an eco-label system on fass.se is a good thing, but there are still large opportunities for improvement.

Another criticism is that pharmaceutical companies have not been sufficiently willing to share data on the environmental impact of pharmaceuticals. This criticism has also been made by the IVL, which expresses it thus in a report:

With a few exceptions, it is unfortunately not common to disclose or make the results publicly available. Among the reasons to not publish results may include confidentiality issues which hamper the possibility for full transparency of the study and results, or that the studies have been made for a specific goal and scope and therefore results are not comparable or relevant to disclose to the public. [48]

One actor who has criticised the pharmaceutical companies for not being sufficiently transparent is Cecilia de Pedro, Sustainability Manager at Apotek Hjärtat. She says: 'We believe it is highly problematic that the industry does not want to share any data because then there is no way to understand the current situation and to improve the situation going forward'. It will be difficult for us and other purchasers to encourage suppliers who have better environmental and sustainability work. Transparency is the beginning of everything.'

5.4 Origin marking

Today there is no requirement for origin marking of medicinal products. In other words, manufacturers are under no obligation to indicate where the products are manufactured. It is possible to request the information for research purposes, but in practice there is no transparency. The 'manufacturer', or country of origin, is indicated on the package leaflet; however, this does not relate to the actual producer, because in the definition in the EU Directive, the importer is defined as a manufacturer. This is a flaw in the EU legislation, which the Swedish Medical Products Agency wants to change.

When an original version of a drug is replaced with a cheaper generic copy, it often has negative environmental consequences, according to research from Chalmers University in Gothenburg[49]. These preparations are often manufactured in countries with, in general, less restrictive environmental laws and poorer environmental control and follow-up, in part due to corruption. This is a strong argument in favour of calls for transparency in the production of pharmaceuticals.

48 https://www.ivl.se/download/18.2299af4c16c6c7485d01de/1565693701749/B2352.pdf

49 https://www.life-time.se/forskning/studie-dags-vaga-in-miljo-i-val-av-lakemedel/

6 Environmentally harmful pharmaceuticals in our waters

6.1 The limits set by the Swedish Agency for Marine and Water Management

To ensure that Sweden has good water quality standards, Sweden's surface water is measured and classified. Good ecological water status means, inter alia, that the concentrations of river basin-specific pollutants (RBSP) in a body of water must not exceed that stipulated in the Regulations of the Swedish Agency for Marine and Water Management on the Classification and Environmental Quality Standards of Water[50].

Environmental quality standards for water are a legal tool; for example, for water to be assessed to be of good quality, the concentration of diclofenac must not exceed 0.1 micrograms per litre in inland waters, and 0.01 micrograms per litre in coastal sea surface water. The the Swedish Agency for Marine and Water Management has decided that diclofenac, estradiol, ethinylestradiol and ciprofloxacin must be considered as river basin-specific pollutants. This makes Sweden the first country to introduce assessment criteria for these substances. However, there is no requirement for authorities or others to make systematic measurements of these substances in water and if limits are exceeded, there are no resultant consequences.

The following are the limit values of the Swedish Agency for Marine and Water Management for the substances in which we are interested. An annual average or maximum concentration below these levels is considered to give 'good ecological status'.

	Inland surface water (surface water in watercourses andlakes) in micrograms per litre of water	Coastal waters and transitional waters inmicrograms per litre of water
Diclofenac (annual average)	0.1	0.01
Ciprofloxacin (maximum value)	0.1	0.1
17-alpha-ethinylestradiol (annual average)	0.000035	0.000007
17-beta-estradiol (annual average)	0.0004	0.00008

6.2 Sales of diclofenac

In this report, Svenskt Vatten presents figures for current sales of diclofenac in Sweden in 2019. The figures, which have been commissioned by the Swedish eHealth Authority, show that in 2019 a total of 4,413 kilos of diclofenac were sold. The over-the-counter gel is equivalent to 2,186 kilos. We have focused on diclofenac because it is the only pharmaceutical in Sweden that is sold without a prescription whilst also being a river basin-specific pollutant.

50 https://www.havochvatten.se/hav/vagledning--lagar/foreskrifter/register-vattenforvaltning/klassificering-och-miljokvalitetsnormer-avseende-ytvatten-hvmfs-201925.html

Diclofenac sold through pharmacies or outside pharmacies in grams

	2019
Cutaneous and transdermal	2,185,902
Oral solid	2,106,583
Parenteral	6,851
Rectal	113,951
Eyes	88
	4,413,375

Source: eHealth Authority

According to the Swedish Medical Products Agency, more than 300,000 patients in Sweden are prescribed diclofenac. In addition, some 3.5 million packs of preparations containing diclofenac are sold without a prescription[51].

How much diclofenac is there in a tube of gel?

Gel containing diclofenac is sold in various sized tubes containing different concentrations of the active substance. A tube of Voltaren containing 100 grams of gel is sold without a prescription by Apoteket for SEK 195. This contains 23.2 milligrams per gram, i.e. 2,320 milligrams of diclofenac. A tube of Orifarm containing 50 grams of gel costs SEK 49 and contains 11.6 milligrams of diclofenac per gram, i.e. 580 milligrams of diclofenac.

How much diclofenac passes into a waste water treatment plant?

Based on the sales figures, we know how much diclofenac is purchased in Sweden in one year; in 2019 4,413 kilos of diclofenac are purchased – of which the over-the-counter gel accounts for 2,186 kilos. We can thus calculate a theoretical average of how much diclofenac in gel is received by individual treatment plants in Sweden. We focus on the gel because it will still be sold over the counter after June 1, 2020.

Our calculation is based on the assumption that every person aged between 15 and 99 years uses on average 0.28 grams of diclofenac via gel per year (7.8 million inhabitants; gel containing diclofenac is not recommended for children under 14 years of age).

Table 1. Estimated quantity of diclofenac from gel, received by treatment plant per year*

	Number of people connected, population equivalents PE	Amount of diclofenac (g)
Lund, Källby treatment plant	100,000	28,000 (28 kg)
Örebro, Skebäck	137,000	38,360 (38 kg)
Uppsala, Kungsängsverket	187,000	52,360 (52 kg)
Borlänge Waste water Treatment Plant	50,000	14,000 (14 kg)
Umeå Waste water Treatment Plant	80,000	22,400 (22 kg)

The calculations are based on the assumption that the entire contents of a tube/package has been used in the same year.

A treatment plant such as Källby in Lund, serving 100,000 connected people, will according to the calculation, receive 28 kilos of diclofenac per year, while Kungsängsverket in Uppsala will receive about 52 kilos.

51 https://www.lakemedelsverket.se/globalassets/dokument/publikationer/miljo/lakemedelsverkets-miljout- redning-2018.pdf

If we were to fill the Globe Events Arena with water...

Just one of the large tubes of diclofenac is sufficient to exceed the limit for good ecological status for coastal waters in as many as 232 x 25m pools (a 25m pool contains 1,000 cubic metres of water). The smaller tube, with the lower concentration of diclofenac, causes the concentration in 60 x 25m basins to increase above the limit for coastal water.

In Sweden we have about 450 public swimming pools, which often have a 25m swimming pool. Some of these public swimming pools have several swimming pools, such as a smaller children's paddling pool. We therefore make the assumption that in Sweden there is the equivalent of 560 municipal 25m pools. Based on this assumption, they together have a total water volume of 560,000 cubic metres. How many diclofenac gel tubes are needed for the concentration of diclofenac to exceed the 'good ecological status' limit for coastal surface waters in all the country's public swimming pools? The answer is ten small tubes or 2.5 large.

We can also put it this way: The Globe Arena in Stockholm has a volume of 605,000 cubic metres, which means that as little as 11 of the smallest tubes, or three of the largest tubes, are sufficient to exceed the limit for good ecological status for coastal waters. This can be compared with the fact that in 2019 more than one million tubes of diclofenac were sold in Sweden.

The calculations are based on the assumption that the entire contents of a tube/package have been used in one year.

When we compare with the actual measured concentrations of diclofenac in waste water treatment plants, we see some variation. One possible explanation could be that more diclofenac is sold than is actually used or that diclofenac is degraded in the human body. Another explanation may be that when the samples of waste water have been taken in the treatment plants, the waste water flows have been higher than the estimated Swedish annual average waste water flow.

How much diclofenac can Swedish lakes, watercourses and coastal waters tolerate?

How much diclofenac is received on average by all the Swedish treatment plants today? We calculate that we use an average of 0.28 grams gel (280,000,000 nanograms of diclofenac) per person per year, and that in Sweden we produce an average of 125 cubic metres of waste water per person per year[52]. This means that in Sweden the waste water received contains an average of 2,240 nanograms of diclofenac per litre of water from the gel alone. Furthermore, calculating that, with today's technology, the treatment plants have capacity to purify less than 10% of diclofenac because it is so difficult to degrade using the treatment plants' normal biological processes, means that the discharged waste water contains 20 times the limit for watercourses and lakes (100 nanograms per litre of water) and 200 times the limit for coastal water (10 nanograms per litre of water). On average, to avoid the risk of exceeding the limit for good ecological status in the watercourse, lake or coastal waters, the water from Swedish treatment plants must be diluted 20 times if discharged to watercourses and lakes, and 200 times if discharged to coastal waters. And this applies only to diclofenac from gel. If we include the tablets, double the dilution is needed.

Many Swedish rivers, lakes and coastal waters have particularly good mixing conditions which means dilution takes place quickly. But, far from all of them. During the summer, many of the Swedish watercourses, into which the treatment plants discharge, have particularly low dilution rates giving a significantly increased risk of exceeding the limits for good ecological status. Watercourses or coastal waters with particularly low dilution rates can tolerate only a 20th or a 200th part of today's use of diclofenac gel. The use of gel therefore needs to decrease by at least a factor of 20 in these cases.

52 https://www.scb.se/contentassets/4d4d22ee07cf4baa9f47e5bab805c00c/mi0106_2016a01_sm_ mi22sm1801.pdf

A calculation of discharge – high concentrations in tourist areas

In 2018, on behalf of the Swedish Environmental Protection Agency, SMED (Svenska MiljöemissionData) calculated[53] the potential discharge of diclofenac, 17-beta-estradiol and 17-alpha-ethinylestradiol from treatment plants to sub-basins. They then calculated the potential concentration of these three substances in the receiving sub-basins. The results were based entirely on calculations, i.e. not measurements, but they nevertheless highlighted some interesting factors.

The calculations show that: 'the waste water treatment plants with the highest number of connected population equivalents and thus the highest load (kg/year) of pharmaceutical residues in inlet and outlet waste water were Ryaverket (Gothenburg), Henriksdal, Käppalaverket (Stockholm) and Sjölunda waste water treatment plants (Malmö).

The results also show that, of the plants with the highest estimated concentration in outlet waste water, almost all were located in tourist areas (Tandådalen, Ransby-Branäs, Björnrike, Kläppen, Sälfjället, Böda and Vimmerby). The difference in estimated concentration in outlet waste water between the various waste water treatment plants depends mainly on the number of connected population equivalents in relation to outlet flow.

The estimated concentration in the sub-basin was higher than the limit for the annual average content of river basin-specific pollutants (RBSP) in surface water in 56 sub-basin areas for diclofenac, 12 sub-basin areas for estradiol and 24 for ethinylestradiol. To confirm the results, actual measurements should be carried out in these sub-basins.

6.3 Measurements by the waste water treatment plants

In this report, we have compiled the measurements made by the treatment plants on the pharmaceuticals that we are interested in. Our compilation only gives a snapshot of the situation, but nonetheless illustrates the levels at which the substances are present in the treatment plants after daily sampling on a few occasions. In some cases, the concentrations of pharmaceuticals are higher in the outlet water from the treatment plant than in the inlet water. This might be because it may be more difficult for the analytical method to detect the parent substance in the inlet water than in the outlet water because the conjugate has been broken down. As shown in the tables (below), several treatment plants measure clearly detectable concentrations of these environmentally harmful substances. The concentrations in outlet water are in several cases higher than the limits for good ecological status in lakes, watercourses, and coastal waters.

There is a large difference, a factor of 35, between the theoretically calculated concentrations of diclofenac in the inlet waste water above (2,240 nanograms of diclofenac per litre water, gel form only) - and the measured concentrations of diclofenac in the inlet waste water in the tables below. We do not have a complete explanation for this difference. Three explanations are possible:

— More diclofenac gel is sold each year than is used each year.
— When sampling the inlet waste water in the treatment plants, the waste water flows have been higher than the estimated Swedish annual average waste water flow.
— Diclofenac is broken down in the human body.

53 http://naturvardsverket.diva-portal.org/smash/record.jsf?pid=diva2%3A1369677&dswid=-6518

Diclofenac

	In inlet water to water treatment plants (nanograms per litre)	In outlet water from water treatment plants (nanograms per litre)
Himmerfjärdsverket, Stockholm (v 9, 2019)	890	860
Himmerfjärdsverket, Stockholm (v 14, 2019)	960	780
Himmerfjärdsverket, Stockholm (v 26, 2019)	1,200	1,100
Sundet Waste water Treatment Plant, Växjö (2019)	860	876
Kungsängsverket, Uppsala (2016)	860	688
Nykvarn Waste water Treatment Plant, Linköping (141106)	560	data lacking
Nykvarn Waste water Treatment Plant, Linköping (141109)	700	data lacking
Nykvarn Waste water Treatment Plant, Linköping (141111)	540	data lacking
Nykvarn Waste water Treatment Plant, Linköping (2015)	data lacking	480
Käppalaverket, Lidingö (2019)	1,200	1,100
Kungsängsverket, Västerås (2016)	1,482	1,647
Ryaverket, Gothenburg (2017-2018)	715*	650**
Ullared Waste water Treatment Plant (v 2, 2019)	1,300	1,300
Ullared Waste water Treatment Plant (v 18, 2019)	1,600	4,100
Ullared Waste water Treatment Plant (v 26, 2019)	1,000	1,000
Ullared Waste water Treatment Plant (v 50, 2018)	1,200	1,100
Skebäcksverket, Örebro (2019)	240	660
Växjö (2019)	860	876

*mean value four-day samples **mean value two-day samples

17-alpha-ethinyl-estradiol

	In inlet waste water to treatment plants (nanograms per litre)	In outlet water from treatment plants (nanograms/litre)
Himmerfjärdsverket, Stockholm (v 9, 2019)	3.5	0.5
Himmerfjärdsverket, Stockholm (v 14, 2019)	2.5	1
Himmerfjärdsverket, Stockholm (v 26, 2019)	2.5	0.5
Sundet Waste water Treatment Plant, Växjö (2019)	data lacking	data lacking
Kungsängsverket, Uppsala (2016)	data lacking	data lacking
Nykvarn Waste water Treatment Plant, Linköping (141106)	data lacking	data lacking
Nykvarn Waste water Treatment Plant, Linköping (141109)	data lacking	data lacking
Nykvarn Waste water Treatment Plant, Linköping (141111)	data lacking	data lacking
Käppalaverket, Lidingö (2019)	data lacking	data lacking
Kungsängsverket, Västerås (2016)	data lacking	data lacking
Ryaverket, Gothenburg (2017-2018)*	<20	<1.2
Ullared Waste water Treatment Plant (v 2, 2019)	10	0.5
Ullared Waste water Treatment Plant (v 18, 2019)	3.5	0.5
Ullared Waste water Treatment Plant (v 26, 2019)	10	1
Ullared Waste water Treatment Plant (v 50, 2018)	45	0.6
Skebäcksverket, Örebro (2019)	data lacking	data lacking
Växjö (2019)	data lacking	data lacking

*mean value four-day samples

17-beta-estradiol

	In inlet waste water to treatment plants (nanograms per litre)	In outlet water from treatment plants (nanograms/litre)
Himmerfjärdsverket, Stockholm (v 9, 2019)	5	1.5
Himmerfjärdsverket, Stockholm (v 14, 2019)	8	1
Himmerfjärdsverket, Stockholm (v 26, 2019)	17	0.5
Sundet Waste water Treatment Plant, Växjö (2019)	5.7	-
Kungsängsverket, Uppsala (2016)	1	-
Nykvarn Waste water Treatment Plant, Linköping (141106)	-	-
Nykvarn Waste water Treatment Plant, Linköping (141109)	-	-
Nykvarn Waste water Treatment Plant, Linköping (141111)	-	-
Käppalaverket, Lidingö (2019)	-	-
Kungsängsverket, Västerås (2016)	-	-
Ryaverket, Gothenburg (2017-2018)*	22	<1.2
Ullared Waste water Treatment Plant (v 2, 2019)	2.5	0.5
Ullared Waste water Treatment Plant (v 18, 2019)	1	0.5
Ullared Waste water Treatment Plant (v 26, 2019)	1.5	1
Ullared Waste water Treatment Plant (v 50, 2018)	8.3	1.5
Skebäcksverket, Örebro (2019)	<10 (2015)	
Växjö (2019)	5.7	

*mean value four-day samples

Ciprofloxacin

	In inlet waste water to treatment plants (nanograms per litre)	In outlet water from waste water treatment plants (nanograms per litre)
Himmerfjärdsverket, Stockholm (v 9, 2019)	3	3
Himmerfjärdsverket, Stockholm (v 14, 2019)	21	3.5
Himmerfjärdsverket, Stockholm (v 26, 2019)	21	1
Sundet Waste water Treatment Plant, Växjö (2019)	50	-
Kungsängsverket, Uppsala (2016)	-	-
Nykvarn Waste water Treatment Plant, Linköping (141106)	<60	<60
Nykvarn Waste water Treatment Plant, Linköping (141109)	<60	<60
Nykvarn Waste water Treatment Plant, Linköping (141111)	<60	<60
Käppalaverket, Lidingö (2019)	-	-
Kungsängsverket, Västerås (2016)	-	-
Ryaverket, Gothenburg (2017-2018)	104*	<5**
Ullared Waste water Treatment Plant (v 2, 2019)	7.5	7.5
Ullared Waste water Treatment Plant (v 18, 2019)	37	37
Ullared Waste water Treatment Plant (v 26, 2019)	85	3
Ullared Waste water Treatment Plant (v 50, 2018)	85	85
Skebäcksverket, Örebro (2019)	5.7	1.3
Växjö (2019)	50	-

*mean value four-day samples **mean value two-day samples

Overview of diclofenac measurements in watercourses and the Baltic Sea

We can present measurements in this report that have not previously been published collectively. These are measurements reported by the Swedish Environmental Protection Agency to the EU Commission in connection with work for the EU Watch List.

The measurements apply to diclofenac in three Swedish watercourses: the rivers Fyris in Uppsala, Höje in Lund and Lövsta in Knivsta. In all these rivers, concentrations higher than the 'good status' limit have been measured, i.e. 100 nanograms per litre of water. The highest concentrations have been measured in the Fyris and Lövsta rivers. We see that the diclofenac concentration is close to the limit in the Höje river, and that this is exceeded for all measurements in the Lövsta river and in two of three measurements in the Fyris river. The maximum concentration for good organic status for diclofenac in freshwater is 10 nanograms per litre of water for coastal waters and 100 nanograms per litre of water for inland waters.

Diclofenac

	Nanograms per litre of water
River Höje	70
River Höje, outlet	93
River Höje	70
River Höje, outlet	114
River Lövsta, 500 m	283
River Lövsta, 2,500 m	172
River Fyris, 150 m	287
River Fyris, 3,500 m	141
River Fyris, 150 m	99

Source: Swedish Environmental Protection Agency

In the case of the Baltic Sea, the status of diclofenac pollution is uncertain. The assessment of diclofenac in the Baltic Sea by the Helsinki Commission (HELCOM) indicates that levels exceed the limit for diclofenac in several coastal locations, but not in open water (insert this reference, as with the other references, with the serial number at the bottom of the page https://helcom.fi/wpcontent/uploads/2020/06/Helcom_170_Diclofenac. pdf reference).

6.4 Measurements of diclofenac in watercourses reported in the VISS database, VattenInformationSystem Sweden (Water Information System Sweden)

According to VISS, VattenInformationSystem Sweden, there is currently a risk in Sweden that limits will be exceeded in 109 bodies of water (= lakes, watercourses, or coastal stretches) for diclofenac, 159 bodies of water for 17-beta-estradiol and 40 bodies of water for 17-alpha-estradiol. Ciprofloxacin is not included in the risk assessment. This is probably due to the inclusion of the substance on the list of river basin-specific pollutants after the Water Authority carried out its impact analysis on pharmaceutical residues. The following Table presents examples taken from the VISS database, VattenInformationSystem Sweden. The Tables present the concentrations of diclofenac above (red colour) or near limits (orange colour) that have been detected at a number of locations, as exemplified below. More samples may be needed to confirm the results.

Name of body of water	Responsible county	Year from	Year to	Number of measure-ments	Observed concentra-tion (µg/L)	Unit of Observed concen-tration	Value in assess-ment basis (µg/L)	Unit of Value in assess-ment basis
Långmyrbäcken (Hissmofors)	Jämtland	2018	2019	2	0.3267	µg/L	0.1	µg/L
Luossajoki	Norrbotten	2016	2019	2	0.25	µg/L	0.1	µg/L
Luossajoki	Norrbotten	2016	2019	2	0.25	µg/L	0.1	µg/L
Bergbäcken	Norrbotten	2016	2016	1	0.2	µg/L	0.1	µg/L
Kaavajoki	Norrbotten	2016	2019	2	0.2	µg/L	0.1	µg/L
Fyris River Jumkil River - Sävja River	Uppsala	2010	2016		0.26	µg/L	0.1	µg/L
Rivö Fjord South	Västra Götaland	2017	2018	5	0.4688	µg/L	0.01	µg/L
Rivö Fjord North	Västra Götaland	2017	2018	5	0.4651	µg/L	0.01	µg/L
River Fria - Horsklippan toBjörkulla	Västra Götaland	2018	2018	1	0.218	µg/L	0.1	µg/L
Lidan - Tovarp toFalköping	Västra Götaland	2018	2018	1	0.21	µg/L	0.1	µg/L
Viskan (from central Borås down toSvaneholm)	Västra Götaland	2017	2018	2	0.19105	µg/L	0.1	µg/L
Ösan - Frösve toSkövde	Västra Götaland	2018	2018	1	0.139	µg/L	0.1	µg/L
Dofsan	Västra Götaland	2018	2018	1	0.135	µg/L	0.1	µg/L
River Tälje (Kvismarecanal) from Näsbygraven's outlet toHammarsån's outlet	Örebro	2016	2016	1	0.09	µg/L	0.1	µg/L
Roxen	Östergötland	2017	2018	2	92.56	ng/L	0.1	µg/L
River Ljuster	Dalarna	2018	2018	2	0.095	µg/L	0.1	µg/L
Kvarnbäcken	Jämtland	2018	2019	2	0.06805	µg/L	0.1	µg/L
River Enköping	Uppsala	2013	2013		0.059	µg/L	0.1	µg/L

Source: VISS

The following are examples of analytical results for individual samples from watercourses in Västra Götaland. Concentrations near or above the limit for ethinylestradiol have been detected in lakes and streams. More samples should be taken to confirm the results. The limit for good ecological status is 0.000035 micrograms per litre of water.

Watercourses	From year	To year	Micrograms per litre
Lidan	2018	2018	0.00003
Bollebygd	2018	2018	0.00005

Source: Jellinek J and Wrande Niklasson C, 2020, Mätkampanj och regional miljöövervakning 2018 - Miljögifter i ytvatten och biota, Länsstyrelsen i Västra Götalands Län [Measurement campaign and regional environmental monitoring 2018 - Environmental toxins in surface water and biota, County Administrative Board of Västra Götaland County].

The following are examples of analytical results for individual samples from watercourses in Västra Götaland. Concentrations near or above the limit for estradiol have been detected in lakes and water courses. More samples should be taken to confirm the results. The limit for good ecological status is 0.0004 micrograms per litre of water.

Watercourses	From year	To year	Micrograms per litre
River Sil	2018	2018	0.00024
River Bäve	2018	2018	0.000371

Source: Jellinek J and Wrande Niklasson C, 2020, Mätkampanj och regional miljöövervakning 2018 - Miljögifter i ytvatten och biota, Länsstyrelsen i Västra Götalands Län [Measurement campaign and regional environmental monitoring 2018 - Environmental toxins in surface water and biota, County Administrative Board of Västra Götaland County].

7 Opinions of the counties' pharmaceutical committees - Survey

In March 2020, we sent out a questionnaire to the chairmen of all 21 county pharmaceutical committees in the country. Even though the survey was sent out during one of the first dramatic weeks of the corona crisis, we received 12 responses in a short time. We wanted to know how doctors with extensive knowledge of pharmaceuticals, their prescription and procurement, viewed environmental aspects when recommending pharmaceuticals. The answers we received strongly concurred on all the questions except one. Some of the most important feedback from the country's pharmaceutical committees is as follows:

- 10 of the 12 doctors who responded think that pharmaceuticals should have eco-labels regarding the release of active substances into the environment during manufacture.
- 10 of the 12 doctors who responded believe that pharmaceutical companies should be required to indicate the countries and factories in which the pharmaceuticals are manufactured.
- 10 of the 12 doctors who responded believe that the country's doctors have insufficient knowledge of the negative environmental impact of pharmaceuticals.
- 11 of the 12 doctors who responded think that pharmaceuticals should be made prescription-only if they are particularly problematic for the environment.
- All 12 doctors who responded believe that TLV should take into account the environmental impact of a pharmaceutical, and not just price, when choosing which pharmaceutical should be the 'product of the period'.
- 10 of the 12 doctors who responded think that all products containing diclofenac should be prescription-only for environmental reasons.

1. Do you think that pharmaceuticals should have some form of eco-label regarding the release of active substance into the environment during manufacture?
Yes 10
No
Don't Know 2

2. Do you think that pharmaceutical companies should be required to become more transparent by requiring them to indicate the countries and factories in which the pharmaceuticals are manufactured?
Yes, for all 9
Yes, for generics 1
No, not at all 1 Don't know 1

3. How much knowledge do you think Sweden's doctors generally have about the negative impact of pharmaceuticals on the environment?
Very good knowledge Sufficient knowledge 1
Insufficient knowledge 10 No knowledge
Don't know 1

4. Does the Pharmaceutical Committee include environmental considerations in pharmaceutical recommendations?
Yes 11
No 1 Don't know
If No, why not? 'small resources…'

5. Do you think that pharmaceuticals should be prescription-only if they are particularly problematic for the environment?
Yes 11
No Don't know 1

6. Do you think that TLV should take into account the environmental impact of a drug, and not just price, when choosing which pharmaceutical should be the product of the period?
Yes 12
No Don't know

7. Do you think that all products containing diclofenac should be prescription-only for environmental reasons?
Yes 10
No Don't Know 2

8. When procuring pharmaceuticals, social requirements are imposed, which also include certain environmental requirements. Many regions also impose additional environmental requirements to a varying extent. Do you think that your region imposes sufficiently high environmental requirements when procuring pharmaceuticals?
Yes 5
No 3
Don't know 4

8 Pharmaceutical treatment and producer responsibility

Removing pharmaceutical residues from waste water is not straightforward. Such cleaning is technically advanced and is energy and resource intensive, and therefore also costly. This makes it also a political issue. In this section, we explain why extended producer responsibility should be introduced in Sweden and the EU and why we believe that the pharmaceutical industry has a responsibility for the costs of removing pharmaceutical residues.

8.1 Cleaning techniques

The burden of pharmaceuticals and other hazardous organic substances in our environment that do not decompose must be reduced. But it is not sustainably possible that, in order to remove pharmaceutical residues, we install advanced waste water cleaning processes in all of Sweden's approximately 1,700 municipal treatment plants. It is therefore important to target those places where the greatest positive environmental impact will be achieved, that is, where emissions are greatest and where there is also an obvious need in the water environment. Today, the country's 21 largest waste water plants clean about 55 percent of Sweden's waste water from urban areas, but the main focus should be on making special efforts inland, where there are vulnerable receiving watercourses as well as downstream areas, and there is a risk that the maximum permissible concentration of the river basin-specific pollutants diclofenac, estradiol, ethinylestradiol and ciprofloxacin will be exceeded.

At the same time, waste water treatment is only part of the solution. Moreover, the fact that use of pharmaceuticals is continuously increasing counteracts the cleaning effects achieved. A wiser use of pharmaceuticals must be applied in parallel. Incentives are therefore needed to motivate pharmaceutical companies, other manufacturers, and importers of environmentally hazardous organic substances to make an effort to produce environmentally friendly products. For example, environmental and sustainability criteria should be included in the pharmaceutical benefits system. Environmentally hazardous pharmaceuticals such as diclofenac should only be sold on prescription.

A number of accepted techniques, such as ozonation and activated carbon/carbon filter techniques (GAC granulated activated carbon or PAC powdered activated carbon), are available to remove pharmaceutical residues from water.

Ozonation

Ozonation is a technique whereby ozone is added to the water that is to be cleaned. The ozone triggers a chemical reaction that oxidizes the pharmaceutical residue. According to the Swedish Environmental Protection Agency, ozonation is a cost-effective way to clean water. It is possible to adjust the amount of ozone used to clean the water depending on the extent of pollution. Ozonation is also stable over time with an instantaneous cleaning rate of 90%. Ozonation is a relatively inexpensive cleaning technique compared to other technologies. Although there are many positive aspects to ozonation, the technology also has drawbacks. Among others, the technology generates by-products which in turn have to be removed. Ozone itself is a hazardous, unstable and highly flammable substance that requires monitoring during use. Furthermore, ozonation is a highly energy-intensive technology.

Ozonation is currently used at a small number of waste water treatment plants in Sweden; it has been used at Linköping for a few years and will soon be used in Tierp. At Nykvarn municipality's modern waste water treatment plant in Linköping, ozonation has been introduced at full scale; at full operation up to 90% of the pharmaceutical residues are removed. Using this technology, there are good technical prerequisites with full scale operations to remove 70-90% of incoming river basin-specific pollutants annually.

The technology is still under development in many places, and has been tested in various projects in several of the country's municipalities. In Haninge, Lidköping and Helsingborg, for example, the Swedish Environmental Protection Agency has recently contributed to the development of ozonation as part of government efforts to develop new treatment techniques.

Activated carbon

Because ozonation creates by-products, combination with other treatment techniques is often recommended. In Europe, ozonation is sometimes combined with activated carbon/carbon filter. Carbon is an effective way to remove pharmaceutical residues from the water. Two types of carbon are primarily used to filter water: granulated activated carbon (GAC) and powdered activated carbon (PAC). The principle is the same for both types of carbon; the substances to be purified attach to the carbon. GAC is designed as a filter and when the carbon is saturated with impurities, it is replaced. The technology is under development, especially in regard to determining when the carbon is saturated with pollutants and the anticipated lifetime. One advantage of GAC is that the old carbon does not need to be discarded but can be reused (regenerated). Using GAC does not consume as much energy as ozonation and has the advantage that by-products are not created; however, producing and regenerating GAC is energy intensive.

PAC is also an effective way to remove pharmaceutical residues from water. In this case, the active carbon is added in powder form to the waste water, but the technology entails high wear and tear on the treatment plants. When water is cleaned, sludge is also produced. If the sludge contains PAC, the possibility of using the sludge as fertiliser on arable land is reduced, and PAC therefore needs to be added and handled in such a way that the treatment process allows separate handling and incineration of PAC sludge to avoid contaminating the other sludge. Regarding the costs of PAC, it is therefore important to bear in mind that all or part of the sludge produced may have to be incinerated, resulting in additional costs and loss of important assets in the sludge. The costs of using carbon filters generally depend on the treatment plants. If a treatment plant already has a sand filter, this can in some cases be combined with a carbon filter. This can reduce investments. Borlänge and Falun have started to invest in activated carbon in waste water treatment funded by grants from the Swedish Environmental Protection Agency. Investments have also been made in activated carbon in Simrishamn and Östra Göinge. In several places in Sweden, there is currently a focus on investigating a combination of ozonation and activated carbon, for example in Umeå, Kungsbacka and Gotland.

8.2 What does it cost?

The water and waste water sector is already facing major future challenges. Major investments are needed in the rehabilitation of older pipe networks, water treatment plants, and waste water treatment plants. In addition, climate change means that municipalities are faced with demands for major new investments to handle storm water. In this context, the question now being asked is: what will it cost to introduce new and advanced technologies that can remove pharmaceutical residues? The water and waste water sector should manage its finances through revenues from the water and waste water tariffs (the costs of water and waste water services are currently financed 99% from water and waste water tariffs). Legislation prevents these being increased to fund capital for future investments in, for example, advanced

treatment of pharmaceutical residues. The difficulties in meeting future investments are greatest for the smaller municipalities and water and waste water organisations.

Exactly what it would cost to install the treatment technology is difficult to assess. In some cases, it may be necessary to remodel the existing area of the treatment plants because the inlet water for pharmaceutical treatment needs to be almost particle-free and contain very low levels of biodegradable substances. The calculations also need to take into account the future operating costs of the new treatment plants. Energy consumption, for example, will increase sharply.

IVL, the Swedish Environmental Research Institute has made an estimate[54] and using it as the basis for our calculation, we get some SEK 1.1 billion in investment costs to expand the treatment at the country's 21 largest waste water treatment plants (larger than 100,000 inhabitants), which accounts for about 55% of the total waste water in Sweden. IVL further estimates that expansion of treatment at the 30 next largest treatment plants (all between 50,000 to 100,000 inhabitants, which cleans about another 20% of the country's waste water) would cost almost as much. Compared to the calculations available in Switzerland and Finland, Svenskt Vatten believes that this estimate is far too low.

The Swedish Environmental Protection Agency[55] has extrapolated the figures for waste water treatment plants serving more than 2,000 people and arrived at an estimated total cost of approximately SEK 2 billion per year for investments in advanced treatment.

The cost per cubic metre of waste water is estimated to be in the range of SEK 0.4 to SEK 1 for treatment plants serving more than 100,000 inhabitants. This corresponds to between SEK 55 and 480 per household per year.

As can be seen, the figures are very uncertain. The Swedish Environmental Protection Agency states regarding the reliability of the assessments: 'Since the specified costs are affected by several parameters and are based on many assumptions, they should be viewed with caution'.

Svenskt Vatten also considers the Swedish Environmental Protection Agency's estimates to be far too low. Rather, the Swedish cost range is expected to be closer to the Swiss and Finnish figures presented below.

If we compare the estimated Swedish investment costs (Naturvårdsverket/ IVL from 2017) with the costs in Switzerland, where the journey to invest in treatment technology has begun, the figure so far is three-four times higher than the Swedish calculations. In the Netherlands, a cost summary was made in 2015 based on experiences from Germany and Switzerland. It showed that advanced treatment would cost almost SEK 3 per cubic metre, depending on the size of the waste water treatment plant (SVU Report 201604). This is also 3 to 5 times higher than the Swedish calculations (Swedish Environmental Protection Agency/IVL).

In Germany, similar calculations have given an estimated cost of approximately SEK 1.20 per cubic metre of waste water. The SVU report writes about the overall estimates from Switzerland, Holland and Germany: 'All cost assessments should be treated with caution: Depending on the costs actually included and what is actually to be achieved, the outcome can be very different. Based on the calculations made in the Netherlands, sizing criteria from Switzerland and Germany, and the costs reported from Germany and Switzerland in particular, a reasonable estimate appears to be somewhere between EUR 0.1-0.3 (equivalent to SEK 1 to 3 per cubic metre'.

In Finland, a 2016 study showed a higher cost than the Swedish calculations (using treatment with a combination technique using activated carbon and ozone). The Finnish example shows costs that are up to seven times higher than the Swedish estimates. It was estimated that advanced treatment of pharmaceutical residues would require investments of between SEK 7 and 14 billion and lead to an increase in the annual operating cost of between

54 https://sjostad.ivl.se/download/18.3016a17415acdd0b1f49cd/1493367986749/C235.pdf

55 https://www.naturvardsverket.se/Documents/publikationer6400/978-91-620-6766-3.pdf?pid=20525

SEK 1 and 2.2 billion. That is, an additional cost for waste water treatment plants serving more than 100,000 people of SEK 4 to 6 per cubic metre. This would mean an increase in water tariffs for Finnish consumers of between 20 to 30 percent.[56]

Potential other costs, in addition to investments and operations, which are not included in the calculations presented above, could include the costs of a new workforce, as well as costs for monitoring, skills supply and the working environment. For some of the treatment techniques described, the knowledge and experience of treatment plant personnel would need to be increased.

In conclusion, it is more likely that the costs of advanced treatment in Sweden will be around SEK 6 to 10 billion for the expansion of 50 to 100 treatment plants.

Treatment of pharmaceuticals can more than double the cost (and energy consumption) of waste water treatment. This means that the total water and waste water rate in some Swedish municipalities may amount to over SEK 10,000 to 15,000 per family per year. For certain groups in society, the water and waste water tariff may thus be higher than the UN recommendation that the water and waste water tariff should be a maximum of five percent of disposable income[57]

The Swedish government has allocated SEK 165 million in grants for advanced waste water treatment for the period 2018-2020, for which municipalities, municipal companies or municipal associations can apply. It is a welcome development initiative, but the money is nowhere near enough for the major investments needed. In this context, the contribution is small and far from sufficient, and may instead be seen as important development money.

If the water and waste water tariffs are not to increase to the levels mentioned above, we must find other ways to finance the investments in treatment techniques that can handle pharmaceuticals. It is not reasonable for the country's water consumers to bear the costs of removing pharmaceutical residues from waste water by themselves.

8.3 Who is to pay? The issue of producer responsibility

Even if we take far-reaching measures, environmentally harmful pharmaceutical residues will end up in our waste water treatment plants. This will require investments in advanced treatment technology, and costs will be high. So who is to pay? The treatment plants? The consumers? The municipalities?

To a large extent today, we have departed from end-of-pipe solutions in environmental policy. That is to say, the idea that any pollutant can be released and that they are then dealt with at the end of the pipes, such as in the treatment plants. In the water and waste water sector we are currently working more with preventive work to stop the use of environmentally hazardous substances. However, in regard to pharmaceuticals, we cannot comprehensively apply this argument because we cannot and do not want to stop using all pharmaceuticals. In some cases, such as in some uses of diclofenac, this can and should be reduced when alternatives are available. But pharmaceuticals are essential, and their overall use will increase rather than decrease in the future.

A well-established and effective principle in environmental work is that the producer should be involved in paying for the management of a product after it has been used – this is known as producer responsibility. Anyone who makes money from the sale of goods on the market should also pay for management of any waste, in whole or in part. This principle applies, for example, to packaging, electronics, cars, batteries and glass.

Svenskt Vatten and EurEau (the European Federation of National Associations of Water

56 https://www.vvy.fi/site/assets/files/1666/jatevedenkasittelyn_teknis-taloudellinen_selvitys_21042016.pdf

57 https://www.un.org/waterforlifedecade/pdf/human_right_to_water_and_sanitation_media_brief.pdf

Services www.eureau.org) believe that those who produce and sell pharmaceuticals – the pharmaceutical industry – must be involved in footing the bill. That is: Sweden and the EU should introduce some form of producer responsibility for pharmaceutical residues.

This issue is highly topical in politics. Several parties in the Swedish Parliament have taken up this issue. For example, the Center Party has proposed the introduction of producer responsibility for pharmaceuticals. The party writes in a motion[58] that 'the municipalities and the water and waste water collective should bear the responsibility for investing in such technology that will also be unreasonably expensive. Instead, a producer responsibility for pharmaceuticals should be introduced... It is also reasonable for pharmaceutical companies to be involved in financing investments in treatment technology to remove pharmaceutical residues in the same way that the packaging industry is responsible for taking care of its own waste'.

There are several models of producer responsibility. For example, the packaging industry charges all producers a fee, and collection is undertaken by a company owned by the industry. The battery model looks similar. Producer responsibility is not shared here, i.e. producers are responsible for the whole chain, from the time the product is placed on the market to recycling/collection. For pharmaceuticals (and other substances in the waste water networks) the situation will be different. Here the treatment (the "collection") will be carried out by the municipal sewage treatment plants. In other words, it must become a shared producer responsibility.

The European organisation EurEau has allowed the possibility of introducing so-called extended producer responsibility within the framework of EU legislation. The report Keep our water affordable: extend producers' responsibility[59] concludes that it is legally possible to incorporate the model of extended producer responsibility into EU law.

It is now a question of defining the legal and financial responsibility for the products that come onto the market and then introducing an appropriate fee for products or substances. The fee shall reflect the treatment costs for waste water treatment plants.

The question is how to do this in practice. The following are the thoughts of EurEau Secretary General Oliver Loebel:

- My personal view is that decision-makers should hand over the management of extended producer responsibility to the pharmaceutical industry, as this sector would be the responsible stakeholder. Fees can be based on the hazard level for a specific substance. The more of a substance a producer places on the market and the more dangerous it is, the higher the fee to be paid.
- I believe that producers should also have a say in deciding how to spend the money, because they have an interest in the most effective solutions. It goes without saying that the measures must be in line with the quality objectives of our waterways.

How do you see the possibility that pharmaceutical companies in Europe will actually take financial responsibility for the harmful effects of their products?

'So far, pharmaceutical companies have shown little willingness to take this responsibility. The concept of extended producer responsibility is quickly gaining ground, not only because the Polluter Pays principle is already embedded in EU law, but also because it is politically and economically reasonable. Therefore, I am cautiously optimistic that, in future, EU legislation will require pharmaceutical companies to take full responsibility for their products,' says Oliver Loebel.

The Läkemedelsindustriföreningen (LIF) does not like the idea of having to pay for the treatment. This is how LIF CEO Anders Blanck writes in an email: The industry is obviously identified as a 'polluter' when emissions occur from our manufacturing processes, but can

58 https://www.riksdagen.se/sv/dokument-lagar/dokument/motion/vatten-va-och-fiske_H7023267

59 http://www.eureau.org/resources/news/398-keep-our-water-affordable-extend-producers-responsibility

it really be that the industry is seen as the polluter when emissions occur from healthcare facilities or as a result of patient excretion? (translated from Swedish) In debates with the EU Commission and in the EU Parliament, other key players have highlighted that it is perhaps rather the care services, the prescribing doctor, the pharmacies that dispense, or even the individual patient, who should be seen as the polluter. And then maybe it's easiest to think of it as the responsibility of society.'

Svenskt Vatten believes that pharmaceutical companies, because they are producers and put products on the market, have a large responsibility. The argument that it is pharmacies, healthcare facilities, or patients who are responsible for the damage is not reasonable. Sweden and the EU should urgently review how extended producer responsibility for pharmaceuticals, with regard to the environment, can be drawn up. The advanced treatment technology required to take care of pharmaceutical residues will cost – and pharmaceutical companies will have to pay.

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