CHALMERS

Environmental Risk Assessment of Pharmaceutical Exposure to Fish in the Swedish Göta Älv River

Master's thesis within the Master´s Programme Sustainable Energy Systems
Examensarbete inom civilingenjörsprogrammet kemiteknik med fysik

ANNA FURBERG

Department of Energy and Environment
Division of Environmental System Analysis
CHALMERS UNIVERSITY OF TECHNOLOGY
Göteborg, Sweden 2014
Report no. 2014:9

REPORT NO. 2014:9

Environmental Risk Assessment of Pharmaceutical Exposure to Fish in the Swedish Göta Älv River

ANNA FURBERG

Department of Energy and Environment
Division of Environmental System Analysis
CHALMERS UNIVERSITY OF TECHNOLOGY
Göteborg, Sweden 2014

Environmental Risk Assessment of Pharmaceutical Exposure to Fish in the Swedish Göta Älv River

ANNA FURBERG

EXAMINER: SVERKER MOLANDER
SUPERVISORS: RICKARD ARVIDSSON, MARIA FLORBERGER

Report no. 2014:9

Department of Energy and Environment
Division of Environmental System Analysis
Chalmers University of Technology
SE-412 96 Göteborg
Sweden
Telephone + 46 (0)31-772 1000

Cover:
Picture showing the Göta Älv river situated in the county of Västra Götaland in Sweden.

Chalmers Reproservice
Göteborg, Sweden 2014

Abstract

The exposure and chronic effects from pharmaceuticals to the assessment endpoint of fish in the Swedish Göta Älv river have been assessed in this study. More specifically, human pharmaceuticals emitted down-the-drain reaching the aquatic environment through waste water treatment plants (WWTPs) have been considered. Both effects of individual pharmaceuticals and mixture effects were evaluated. The geographical exposure of pharmaceuticals was modelled with the Geo-referenced Regional Environmental Assessment Tool for European Rivers (GREAT-ER) and mixture effects were calculated using the concept of concentration addition as a conservative first tier. A habitat comparison was performed by comparing the locations with high concentrations of pharmaceuticals to the locations of known fish habitats. The modelling results were also validated by comparison with measurements of concentrations performed in Swedish rivers.

In total, 12 pharmaceuticals were studied; diclofenac, propranolol, carbamazepine, ethinylestradiol, ibuprofen, metoprolol, gemfibrozil, estradiol, paracetamol, sertraline, verapamil and estrone. These pharmaceuticals have all been detected in Swedish waters and highlighted in studies performed by the Region of Västra Götaland (VGR) and the Swedish environmental research institute (IVL).

The results from this study indicated that the pharmaceuticals, when considered individually, in general might not cause adverse effects to the fish in the Göta Älv river. An exception was gemfibrozil, which may cause adverse effects to fish in some parts of the river. However, when mixture effects were considered, it could be established that adverse effects may occur in parts of the river and that the concentrations of pharmaceuticals in the mixture in general are close to the level at which adverse effects are expected to occur. Two parts of the Göta Älv river catchment were identified as the parts with the highest concentrations of the studied pharmaceuticals. These parts are the tributary Gårdaån in connection to Nygård WWTP and a part close to Älvängen. The habitat comparison showed that these parts are known habitats for the fish species considered.

There are uncertainties in these results due to lack of and uncertainties in data, especially in chronic toxicity data for the assessment endpoints *Salmo salar* and *Salmo trutta*. However, the results can serve as an indication of risk for chronic effects to fish in the Göta Älv river and of the importance of considering mixture effects. Further studies providing site-specific measurements would be required in order to confirm these results.

Keywords

Exposure assessment, effect assessment, GREAT-ER, mixture toxicity, concentration addition, ecological risk assessment, chemical risk assessment

Acknowledgements

I am very grateful for all the help that I have received throughout the work with this master's thesis. Thanks to all of you that have provided me with data for the analysis. I would especially like to thank my examiner Sverker Molander and my supervisors Rickard Arvidsson and Maria Florberger for all your support. I would also like to express my gratitude to Frank Koorman for his support regarding the GREAT-ER program.

Table of contents

1 Introduction

Larger river systems, like the Göta Älv river, flow through a wide range of surroundings like for example cities and agricultural landscapes. Such river systems are recipients for different point sources of contaminants like waste water treatment plants (WWTPs) and industries. Therefore, these river systems can receive a large range of contaminants. There are several WWTPs situated along the Göta Älv river that treat waste water from households. A part of the waste water from for example the municipalities of Älvängen and Kungälv situated along the Göta Älv river is also led to the Rya WWTP in Göteborg (Svensson, 2014). Some of the contaminants, among them pharmaceuticals that are released into the waste water, are treated in these plants. However, there are still toxic substances that pass WWTPs untreated or transformed and are discharged into the recipient (Fick et al., 2011; VGR, 2008). The removal efficiency of chemicals in WWTPs varies and the emissions of different chemicals that may pose a risk to fish and other organisms that live in the river therefore vary as well. The sources and the contaminants can be numerous and because of this it can be difficult to prioritize which sources and contaminants that pose the highest risk to the aquatic environment and thus require mitigation measures.

In the master's thesis study by Westerdahl (2009), pharmaceuticals were identified as posing the highest risk to fish, more specifically to the fish species *Salmo salar* and *Salmo trutta*, in the Göta Älv river. Other chemicals studied were metals, pesticides and organic pollutants. The study concludes that pharmaceuticals may cause adverse effects on the aquatic ecosystem. There are also a lot of known effects of pharmaceutical residues in the environment of which a majority has been reported from studies on fish (VGR, 2008).

Chemicals seldom occur as single substances in the environment, but commonly as mixtures. Despite this fact, legislations such as the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) primarily focuses on the assessment of individual chemicals (Backhaus and Faust, 2012). REACH is a regulation of the European Union that establishes procedures for the assessment of hazards of substances (ECHA, 2014). According to Kortenkamp et al. (2009), there is strong evidence that chemicals with similar modes of action can produce combination or additive effects that are larger than the effects of the individual chemicals. Assessing chemicals individually and thereby neglecting mixture effects might lead to underestimations of the risks to the environment (Kortenkamp et al., 2009).

1.1 Objectives and aim

The main objective of this master's thesis was to assess the risk arising from pharmaceutical exposure to fish in the Göta Älv river in Sweden.

This thesis aim at:

- Providing an estimate of the quantity of the emissions of pharmaceuticals into the Göta Älv river.
- Performing an assessment of the level of exposure of pharmaceuticals to fish in the Göta Älv.
- Evaluating whether the exposure to pharmaceuticals poses a risk to fish in the Göta Älv, both when pharmaceuticals are considered individually and as a mixture.

Hopefully, the study can give support to risk management of contaminants and sources of contaminants in the Göta Älv river. A more long-term aim was to contribute to increased knowledge regarding the risk for adverse effects on aquatic environments from exposure of pharmaceuticals.

1.2 Scope

The study was limited to human pharmaceuticals emitted down-the-drain and to WWTPs as the source for these pharmaceuticals to the environment. Two species, *Salmo salar* (Eng. salmon) and *Salmo trutta* (Eng. trout) that live in the Göta Älv river, were included in this study. These two species has been identified as highly desirable to preserve in the river and were also used as the assessment endpoints in the study by Westerdahl (2009). Göta Älv is a large river and is for example the recipient of the harbour of Gothenburg, which is one of many sources of contaminants to the river. In order to limit the complexity of the study, the studied area was restricted to the stretch from the outflow of lake Vänern into the Göta Älv river in Vänersborg to where the tributary Säveån reaches the river upstream the harbour of Gothenburg (Figure 1). Thus, excluding the northern stretch upstream the outflow of lake Vänern that also belongs to the catchment of the Göta Älv river. The Nordre Älv river, at the division of Göta Älv in Kungälv, was also excluded from this study.

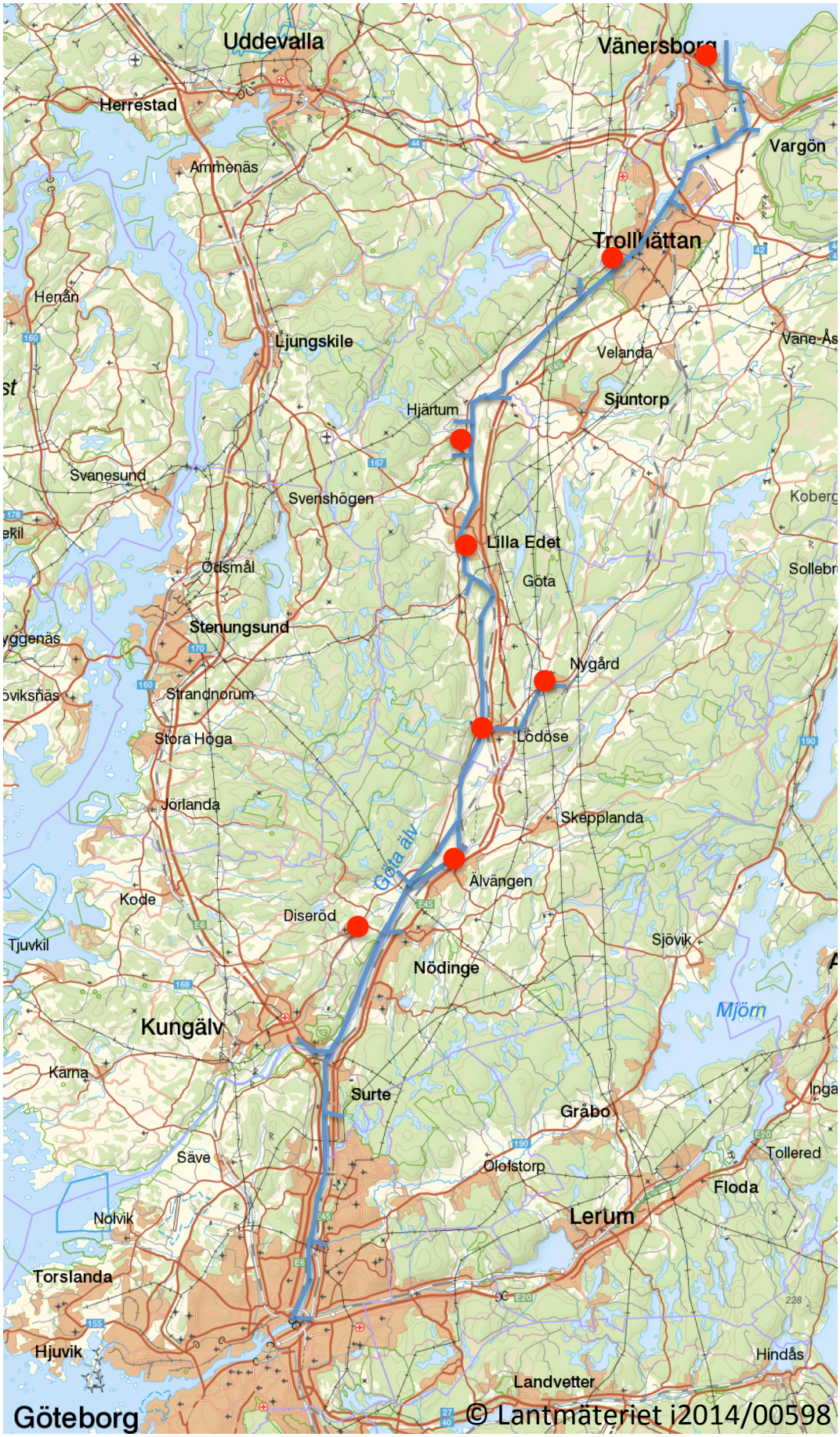


Figure 1: Map showing the geographical scope of the study. The red dots are WWTPs.

2 Background

In this chapter, information about pharmaceuticals in the environment and the Göta Älv river will be presented. Together with a short background on the GREAT-ER model, which was used to simulate pharmaceutical concentrations in the Göta Älv river.

2.1 Pharmaceuticals in the environment

Pharmaceuticals are usually chemically stable or persistent substances. This property is important so that they can be stored and transported without being degraded (SEPA, 2008). The persistency is also important in order to avoid that the pharmaceutical is being metabolized too early in the body and does not reach its primary target organs at a sufficiently high concentration (SMPA, 2013). However, the persistency of pharmaceuticals can be problematic since pharmaceuticals that are not easily degraded can spread over larger areas and concentrate in the environment. Pharmaceuticals that are not completely metabolized in the human body are excreted through urine and faeces and can thereby reach the environment via WWTPs (SMPA, 2013). Metabolization can imply degradation of pharmaceuticals in different ways and order but can also imply transformations of them through for example conjugations. The metabolization could also be due to a combination of degradation and transformation. Pharmaceuticals that are not removed in the WWTP can reach the aquatic environment, but also the drinking water supplies (Kummerer, 2008). Excreted pharmaceuticals that are emitted from WWTPs is the largest source of human pharmaceuticals, used in the health and medical service, to the environment (SMPA, 2013).

There has been an increasing concern for human pharmaceuticals in the environment in recent years. According to Brooks and Hugget (2012), pharmaceuticals are increasingly found in freshwater, coastal ecosystems and in drinking water. Studies from several countries have reported feminization effects on fish downstream WWTPs due to exposure to the endocrine disrupting pharmaceutical ethinylestradiol (VGR, 2008). Ethinylestradiol is also one of the three pharmaceuticals that have been proposed for the water framework directive (WFD) priority list of substances (EC, 2012). The other two are diclofenac and estradiol.

Example of studies on pharmaceuticals in Swedish waters are studies done by the Swedish Environmental Research Institute (Fick et al., 2011), the County Administrative Board of Västra Götaland (VGR, 2008) and Andersson et al. (2006). These studies show that there are several different pharmaceutical residues present in Swedish waters and that some of them are present at such high levels that there is a risk of adverse effects to the aquatic environment. According to the study by Westerdahl (2009), the levels of the pharmaceuticals diclofenac, propranolol, carbamazepine and ethinylestradiol in the Göta Älv river may cause adverse effects to the aquatic ecosystem.

2.2 The Göta Älv river

The Göta Älv river, with an average flow of approx. 550 m^3/s, covers a distance of approx. 93 km from the outflow of Vänern to the ocean (GÄVVF, 2013). The natural drainage area of the Göta Älv river constitutes about a tenth of the total area of Sweden, which makes it the largest natural drainage area of Sweden. Vänern, the largest lake in Sweden, and its tributaries are parts of this natural drainage area.

The Göta Älv river is very important for the county of Västra Götaland, but also for the whole of Sweden. For example, it is an important transportation route and power source and

it serves as a drinking water resource for approx. 800 000 people (GÄVVF, 2013). The drinking water intake is at Lärjeholm. The time it takes for the water to travel from the outflow of Vänern to Lärjeholm is about 1.5 to 5 days (Göransson et al., 2013). Lärjeholm lies approximately five km from where Säveån discharges into Göta Älv, which is the endpoint of the studied part of the Göta Älv river. The river does not only serve human purposes – some of its tributaries are also important spawning areas for salmon and trout (GÄVVF, 2013).

Despite the increasing concern regarding pharmaceuticals in the aquatic environment, no measurements of pharmaceuticals have been performed in the Göta Älv river, known by the author. However, measurements of pharmaceuticals have been performed in other Swedish rivers and for WWTPs in similarly populated areas by Fick et al. (2011) and VGR (2008). Examples of these recipients are the Fyris river in Uppsala and the creek Mörkebäcken in Skövde. The studies done by Fick et al. (2011) and VGR (2008) confirm that pharmaceuticals are present, and sometimes at concentrations that can pose a risk for adverse effects on the aquatic environment.

2.3 The GREAT-ER model

The GREAT-ER model is an advanced environmental exposure model for chemicals in catchments. A catchment can be the natural drainage area of a river. The exposure model estimates concentrations at different geographical locations depending on the flow characteristics of the river. The model is intended for use in for example the European Union water framework directive (WFD) or the European chemical risk assessment process, REACH (Cefic-LRI, 2014). GREAT-ER is applicable, and most suited, to study effects of chemical emissions from point sources, such as WWTPs or industrial production plants. However, there exist a GREAT-ER sediment extension that acknowledges diffuse sources from agricultural run-off (Cefic-LRI, 2014). The model has been validated and used in several studies on down-the-drain-chemicals like pharmaceuticals. Many of these studies will be referred to in the following sections.

2.3.1 GREAT-ER for down-the-drain chemicals

Examples of down-the-drain-chemicals studied in order to validate the GREAT-ER model are detergent ingredients like linear alkylbenzene sulphonate (LAS), boron and the metal zinc (Price et al., 2009; Wind et al., 2004; Schowanek et al., 2001; Hüffmeyer et al., 2009). Furthermore, according to Schowanek and Webb (2002), pharmaceuticals can, after a correction of the excretion fraction of consumed pharmaceuticals from humans, be treated as usual down-the-drain-chemicals. This indicates that the GREAT-ER model is applicable for pharmaceuticals as well.

There also exist several studies that provide an evaluation of the ability of the GREAT-ER model to simulate concentrations of pharmaceuticals in European rivers specifically (Schowanek and Webb, 2002; Alder et al., 2010; Hannah et al., 2009; Aldekoa et al., 2013). Examples of studied pharmaceuticals are ethinylestradiol and paracetamol, and the studied European rivers are located in the United Kingdom, Germany and Italy. These studies compared predicted environmental concentrations (PECs) derived by the GREAT-ER model with measured environmental concentrations (MECs) of human pharmaceuticals such as ethinylestradiol, propranolol and diclofenac in the rivers. The PECs in these studies were generally consistent with the MECs, even though the consistency varied between the studies and between the different pharmaceuticals. The studies concluded that the PEC estimations

using GREAT-ER could be improved if the input data is refined so that uncertainties related to input parameters such as consumption and degradation of the pharmaceuticals are reduced.

If considerable effort is put in deriving input parameters that are reliable and applicable to Göta Älv, it seems reasonable to assume that the GREAT-ER model can predict PECs in Göta Älv with sufficient certainty.

2.3.2 Human health risk assessment of pharmaceuticals with the GREAT-ER model

Human health risk assessment (HRA) regarding human pharmaceuticals in surface waters have been performed using the GREAT-ER model (Cunningham et al., 2009; Cunningham et al., 2010). These studies were done in order to assess risks for humans from exposure to pharmaceuticals in drinking water and from consumption of fish from rivers to which pharmaceuticals are being discharged from WWTPs. European rivers located in the United Kingdom, Germany, France, Italy and Belgium and several pharmaceuticals were included in these studies. The results from these studies showed that there was no considerable risk to human health from exposure to pharmaceuticals via drinking water and fish consumption. However, the study performed by Cunningham et al. (2009) underlined the need to consider how chronic, or long-term, risks can be assessed for humans from exposure to mixtures of trace levels of pharmaceuticals. The conclusion that chronic or long-term effects of mixtures of pharmaceuticals are of interest to investigate further provides an argument for considering mixture effects in this study.

2.3.3 Mixture effects to fish from pharmaceuticals modelled with GREAT-ER

A study that takes mixture effects from exposure to pharmaceuticals into account is the one conducted by Sumpter et al. (2006). In this study, both individual effects and mixture effects from exposure of estrogenic pharmaceuticals to fish in the Aire-Calder catchment in the United Kingdom were investigated and the concentrations in the river were predicted using the GREAT-ER model.

Sumpter et al. (2006) concluded that it is necessary to account for mixture effects when estrogenic pharmaceuticals are considered, since the risk assessments of the individual pharmaceuticals in their study led to underestimations of the risk. The study showed that the pharmaceuticals individually did not pose any significant risk, except ethinylestradiol that was assessed to cause adverse effects in some parts of the river. However, when a mixture of pharmaceuticals was considered, it was assessed to be a risk for negative effects in almost the entire river catchment. The risk was assessed to be high or even severe for the fish in some parts of the river. The study also highlighted the advantage to model pharmaceutical concentrations, since measurements usually are time-consuming and expensive. Especially, when the pharmaceuticals of interest are present at low concentrations in the river and hence particularly difficult to detect.

3 Method

The method that was used in this study is environmental risk assessment (ERA) and the general methodology of ERA will be described in this chapter. The steps of hazard identification, exposure assessment, effects assessment and risk characterization in the ERA of this study will also be described. Finally, a habitat comparison is presented.

3.1 Environmental risk assessment – general method

ERA is a broad term that encompasses a number of more specific methods. Chemical risk assessment (chemRA) and ecological risk assessment (ecoRA) are two specific methods that have provided most inspiration to this study. The general frameworks of these methods will be described in the following sections. The frameworks for chemRA and ecoRA can be divided into a risk assessment part and a risk management part. However, only the risk assessment parts of the two frameworks will be described in following sections since this study was limited to risk assessment.

Stressor and assessment endpoint, or risk object, are two important concepts in ERA. Elements of a system that cause unwanted outcomes are called stressors (Burgman, 2005) and can be chemical, physical or biological. Typically the stressor is a chemical in chemRA and can be many different things in ecoRA. The assessment endpoint is what should be protected and what the potential risk should be evaluated for. In chemRA the assessment endpoint can be the environment or humans (van Leeuwen and Vermeire, 2007) while it is the environment, the ecosystem or particular species that constitute the endpoint in ecoRA (Suter II, 2006).

3.1.1 Chemical risk assessment

The framework for chemRA (Figure 2) is based on *Risk assessment of chemicals: An introduction* by van Leeuwen and Vermeire (2007). The risk assessment part of the framework consists of four different steps; hazard identification, exposure assessment, effect assessment and risk characterization. Human risk assessment (HRA) has been the main focus for risk analysis historically. However, it has gradually become more evident that environmental pollution also should be considered. The framework for chemRA can be used to assess the risk both for human health and for the environment.

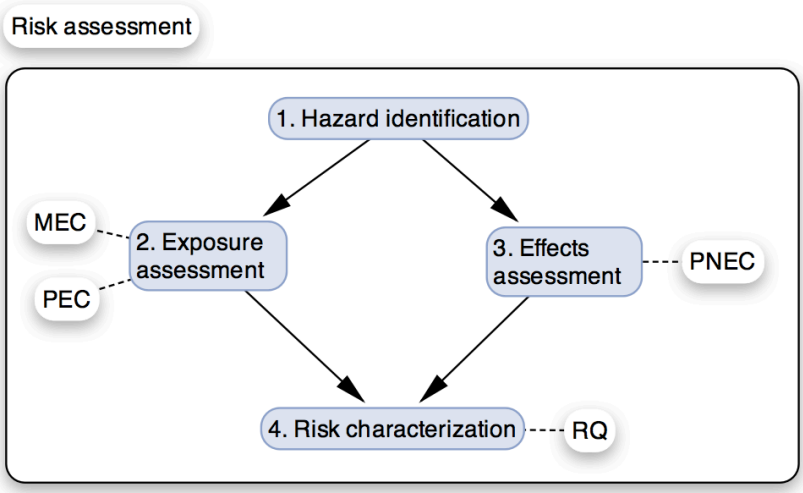


Figure 2: Framework for chemRA based on van Leeuwen and Vermeire (2007). Only the risk assessment part of the framework is presented. The abbreviations are the measured environmental concentration (MEC), predicted environmental concentration (PEC), predicted no effect concentration (PNEC) and risk quotient (RQ).

Hazard identification (step 1)

In the first step of chemRA, information is gathered and evaluated concerning potential effects that a chemical can induce and under which exposure conditions these effects will be produced. The assessment endpoint or the risk object, that is the entity that should be protected, is also identified. There is no risk if the environment or the assessment endpoints are not exposed.

Exposure assessment (step 2)

The chemical exposure can be assessed by measuring environmental concentrations (MECs) or by predicting environmental concentrations (PECs), for example through modelling. PECs are obtained by estimating emissions, potential transportation and exposure pathways, rates of migration and uptake of a chemical. The transformation and degradation of the chemical also have to be considered. It can be quite difficult to accurately estimate emissions from production and the use of chemicals and the variability of exposure in time. The exposure also varies with geographic conditions due to variations in climate, hydrology, geology and ecosystem structures and functions. This contributes to the uncertainty in exposure assessments of chemicals.

Effects assessment (step 3)

Effects assessment evaluates the relationship between a certain exposure to a chemical and the occurrence, rate, frequency and severity of an effect. This relationship is called the dose-response or concentration-response relationship. The dose-response relationship may be different for short-term and long-term exposure. That is, acute effects or chronic effects might occur. Toxicity data describing the dose-response or concentration-response relationship for a chemical and a certain type of organism are usually gathered from experiments and laboratory studies. Generally, the toxicity data must be extrapolated to be valid for the assessment endpoint and studied system since experimental data are typically from model systems and species that do not fully correspond to the actual environmental system studied. So called uncertainty factors or assessment factors (AFs) can be used in order to account for the uncertainties in extrapolating toxicity data gathered in the lab to the ecosystem level. Applying AFs to toxicity data is one common way to obtain predicted no effect concentrations (PNECs) for a specific chemical and assessment endpoint.

Risk characterization (step 4)

In this step the risk is characterized. The occurrence, rate, frequency and severity of the adverse effects likely to occur in the assessment endpoint due to exposure to a chemical are estimated. Risk characterization requires integration of step 1 to step 3. Uncertainties and assumptions from the earlier steps are considered and the magnitude of the risk is assessed. Many international frameworks precise environmental risks through deriving risk quotients (RQs) of PECs to PNECs. RQ does not provide an absolute measure of risk, but the likelihood for adverse effects increases with increasing RQ.

3.1.2 Ecological risk assessment

The U.S. EPA framework is the most commonly used framework for ecoRA (Figure 3). This framework for environmental assessment is presented in this section and based on *Ecological risk assessment* by Suter II (2006).

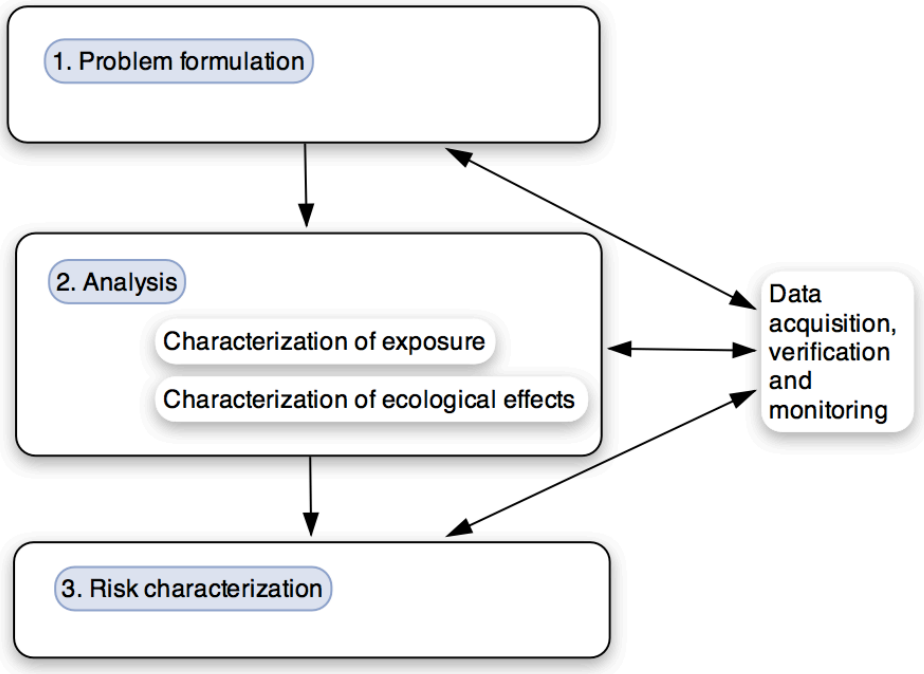


Figure 3: The U.S. EPA framework for ecoRA based on Suter II (2006). Only the risk assessment part of the framework is presented.

Problem formulation (step 1)

In step 1, contaminants, assessment endpoints, or risk objects, and the exposure pathways are identified. Information regarding the contaminants, sources, effects and the receiving environment is gathered. A conceptual model, describing the relationship between sources and the endpoint receptors, is developed. An analysis plan is also developed for how the required data should be obtained and how the risk assessment should be performed.

Analysis (step 2)

In the analysis step, a technical assessment is performed. This assessment considers exposure and effects. The exposure is characterized by evaluating results of exposure measurements and through estimating the spatial and temporal distribution of the exposure. The effects are characterized by assessing indications of responses to the assessment endpoint arising from a certain exposure.

Risk characterization (step 3)

The results from the analysis step are in step 3 integrated in order to estimate and explain the risk. This step involves implementation of an exposure-response model and analysis of uncertainties.

3.1.3 Other assessment methods

Risk assessment is applicable in a broad range of environmental decision-making procedures. Risk assessment, ecoRA and chemRA specifically, can be seen as parts of a larger family of methods for environmental system analysis (Finnveden and Moberg, 2005). Sometimes there are other types of assessments that are more appropriate to use than risk assessment methods or methods that are more commonly used in some situations (Suter II, 2006). Examples of other assessment methods are life cycle assessment (LCA), programs for monitoring status and trends in the environment, legally enforced standards and environmental impact assessment (EIA) (Suter II, 2006).

3.2 Hazard identification

The conceptual model that was used in this study is presented in this section. The selection of stressors, or more precisely the pharmaceuticals, in this environmental risk assessment, is also described.

3.2.1 Conceptual model

This section presents and describes the conceptual model that has been used in this study (Figure 4). The conceptual model can be divided into four different steps; purchase and consumption, the sewer, the WWTP and the river. The contents of each step will be thoroughly described in this section that ends up with a shorter description of what has been excluded from the conceptual model and with a list of the parameters used in the conceptual model (Table 1).

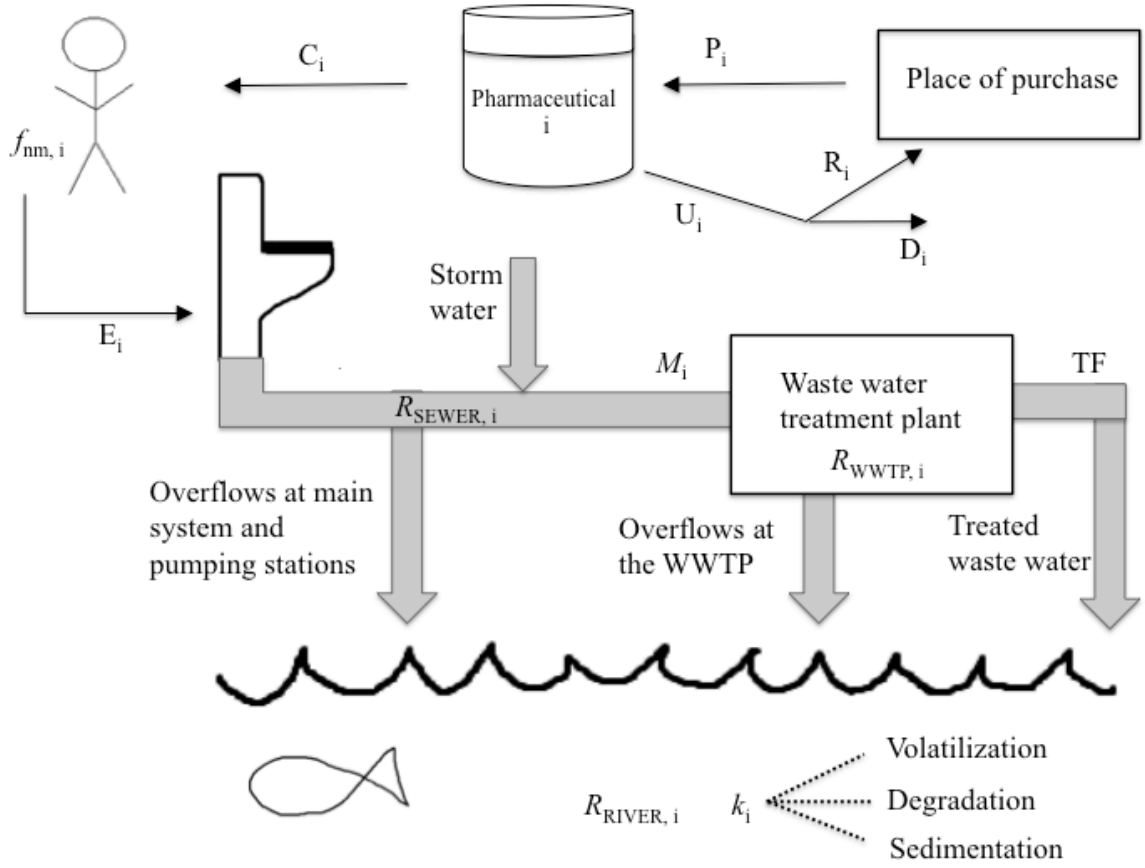


Figure 4: Conceptual model. Descriptions of the parameters can be seen in Table 1.

Purchase and consumption

In the first step of the conceptual model, a pharmaceutical denoted i is purchased (P_i) for example at a pharmacy or food store. The pharmaceuticals that are purchased are usually not equal to the pharmaceuticals that are consumed (C_i), because some of the pharmaceuticals are never consumed, equation [1]. The unconsumed pharmaceuticals (U_i) are either discarded (D_i) or returned (R_i), for example to the place of purchase where they are taken care of, equation [2]. The discarded pharmaceuticals can, however, reach the Göta Älv river if they are disposed of in the sewer.

$$C_i = P_i - U_i \quad [1]$$

$$U_i = D_i + R_i \quad [2]$$

Sewer

All of the consumed pharmaceuticals are not emitted into the sewer. This is because the pharmaceuticals that are used are perhaps not fully metabolized in the human body. Therefore, only a part of the consumed pharmaceuticals are excreted into the sewer, or so-called down-the-drain, through urine and faeces (SMPA, 2013). The amount of pharmaceuticals that enters the sewer through excretion (E_i) is hence the fraction of the pharmaceutical that is excreted ($f_{nm,i}$) times the amount that is actually consumed (C_i), equation [3]. Sewage water, including the excreted pharmaceuticals together with flush water and in some sewer systems storm water, flows through the sewer. There is a possibility that there is some removal of pharmaceuticals in the sewer ($R_{SEWER,i}$). The consumed pharmaceuticals that finally reach the WWTP (M_i) can therefore be described with equation [4].

$$E_i = f_{nm,i} \cdot C_i \quad [3]$$

$$M_i = E_i \cdot (1 - R_{SEWER,i}) \quad [4]$$

WWTP

Sometimes, not all of the incoming waste water is treated in the WWTP. This is for example the case at times when the flow is too large for the plant to handle. There can also be overflows at the main system and pumping stations that are pumping the waste water to the WWTP. The pharmaceuticals in the sewage water that actually is treated are removed to various extents. The removal is depending on the removal efficiency for each pharmaceutical ($R_{WWTP,i}$) in the plant. The discharge of pharmaceuticals at the WWTP to the river can be divided into two parts and one of them is the treated effluent. The fraction of the pharmaceutical in the influent that is treated (*TF*) varies between different WWTPs. The other part is the untreated waste water, due to overflows at the WWTP. The total release of pharmaceuticals into the river at the WWTP, equation [5], will be a combination of the amounts of pharmaceutical *i* in the overflow and the treated flow ($M_{out,i}$).

$$M_{out,i} = M_i \cdot (1 - TF) + M_i \cdot TF \cdot (1 - R_{WWTP,i}) \quad [5]$$

River

The amount of pharmaceutical *i* that is released into the river from the waste water treatment plant ($M_{out,i}$) is diluted and degraded to various degrees. The in-stream removal of pharmaceutical *i* ($R_{RIVER,i}$) is calculated according to section 3.3.3 using the in-stream removal rate (k_i), which is for pharmaceutical *i*. The dilution of the effluent from the WWTP varies since the flow in the river varies, due to for example precipitation. The in-stream removal of pharmaceuticals can for example be due to degradation, sedimentation and volatilization. For the selected pharmaceuticals the sedimentation in Göta Älv and volatilization are considered to be non-significant, see section 3.3.7. Fish living in the river can then be exposed to the discharged and non-degraded pharmaceuticals. The pharmaceuticals can be taken up by the fish and exert toxicity.

Delimitation of the conceptual model

Emissions from other sources than down-the-drain are not considered in this study. Examples of excluded sources and other exclusions:

- Release from agriculture (do not consider veterinary pharmaceuticals).
- Direct release from the pharmaceutical industry (no manufacturing of pharmaceuticals along the river).
- On-site sewage systems (15 % of the population in Sweden were not connected to waste water collection systems in 2002 (van Leeuwen and Vermeire, 2007)).
- Metabolites of pharmaceuticals.

Table 1: Description of the parameters for the conceptual model.

Parameter	Symbol	Unit
Purchased pharmaceutical *i*	P_i	kg/(capita · year)
Consumed pharmaceutical *i*	C_i	kg/(capita · year)
Amount of pharmaceutical *i* that is unused	U_i	kg/(capita · year)
Amount of pharmaceutical *i* that is discarded	D_i	kg/(capita · year)
Amount of pharmaceutical *i* that is returned, for example to the place of purchase	R_i	kg/(capita · year)
Amount of pharmaceutical *i* that is excreted into the sewer	E_i	kg/(capita · year)
The fraction of the consumed pharmaceutical *i* that is not metabolized in the body but excreted	$f_{nm,i}$	-
In-sewer removal of pharmaceutical *i*	$R_{SEWER,i}$	-
Consumed amount of pharmaceutical *i*, the quantity that enters the WWTP	M_i	kg/(capita · year)
Average removal of pharmaceutical *i* in the WWTP	$R_{WWTP,i}$	-
The treated fraction of the flow through a WWTP	TF	-
The total release of pharmaceutical *i* from the waste water treatment plant including both overflows and treated pharmaceutical flows at the WWTP	$M_{out,i}$	kg/(capita · year)
In-stream removal of pharmaceutical *i*	$R_{RIVER,i}$	-
In-stream removal rate of pharmaceutical *i*	k_i	1/h

If the quantity of consumed amounts of pharmaceuticals that enters the WWTP (*M*) is obtained using backward calculation, see section 3.3.5, then the purchase and consumption step and the sewer step can be excluded from the calculations and effectively from the conceptual model. If *M* on the other hand is obtained using forward calculation, see section 3.3.6, the purchase and consumption step and the sewer step is considered in the calculations and is still implicitly included in the conceptual model.

3.2.2 Stressor selection

According to FASS (2014), there exists approx. 1 200 active substances in the approx. 8 300 approved pharmaceuticals in Sweden. Among these, 7 700 are human pharmaceuticals and the rest are veterinary pharmaceuticals. Because of the large number of different active substances in the approved pharmaceuticals in Sweden, the amount of pharmaceuticals to assess had to be limited. Therefore, a strategy for the selection of pharmaceutical substances to include in the study was developed. Examples of selection criteria were 1) toxicity to or mode of action relevant for fish and 2) data availability. The stressor selection strategy that was developed and used in this study is presented in Figure 5.

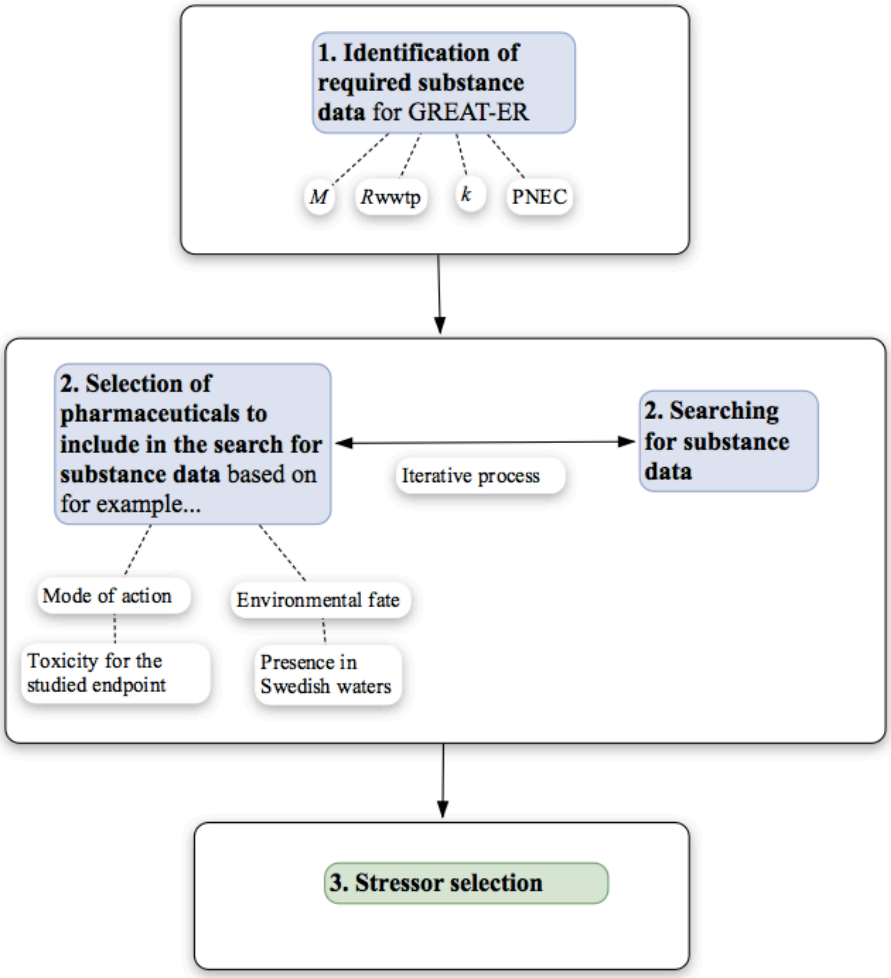


Figure 5: Stressor selection strategy. *M* stands for the consumption of pharmaceuticals that enters the WWTP and R_{WWTP} is the removal efficiency of pharmaceuticals in the WWTP. *k* is the in-stream first order removal rate of pharmaceuticals and PNEC stands for the predicted no effect concentration.

Identification of required substance data

The stressor selection was initialized by an identification of the type of substance input data required for the GREAT-ER model. In total, four input parameters were identified:

1) the consumption of pharmaceuticals (*M*), that is the quantity of pharmaceuticals that enters the WWTP,
2) the average removal efficiency of pharmaceuticals in the WWTP (R_{WWTP}),
3) the in-stream first order removal rate of pharmaceuticals (*k*), and
4) the predicted no effect concentration (PNEC) for the studied endpoints *Salmo salar* and *Salmo trutta*.

The input parameters are described further in section 3.3.

Selection of pharmaceuticals to include in the search for substance data

After the identification of the required substance data for the modelling, the pharmaceutical substances to do the data search for were selected. Because it was difficult to find substance data, the stressor selection had to be an iterative process. Pharmaceuticals were therefore chosen based on 1) their relevance for the chosen assessment endpoint fish, that is for example their mode of action, presence in the environment and environmental fate, but also 2) based on whether substance data for the chosen pharmaceuticals could be found.

The selection of substances to include in the search for substance-specific data was first based on the two reports *Results from the Swedish National Screening Programme 2010,* (Fick et al., 2011), and *The environmental influence of pharmaceuticals. Report – Mapping pharmaceutical residues in Västra Götaland,* (VGR, 2008). These reports studied in total 191 pharmaceuticals and constituted an important basis for the selection of substances. These studies were conducted in Swedish waters and included information about R_{WWTP} of pharmaceuticals in Swedish WWTPs, which was a required input parameter for GREAT-ER (Figure 5).

In the study performed by the Swedish Environmental Research Institute (IVL) (Fick et al., 2011), MECs in Swedish waters were compared to so-called critical environmental concentrations (CECs), which are surface waters concentrations that theoretically could cause pharmacological effects in fish. From this procedure, 15 pharmaceuticals out of the 101 were highlighted as likely to cause pharmacological effects in fish based on MECs of pharmaceuticals. Five of these pharmaceuticals were measured at levels expected to cause pharmacological effects in fish and the other ten were measured close to levels expected to cause pharmacological effects. All 15 pharmaceuticals were selected to be included in the search for substance data except clarithromycine that is an antibiotic (Table 2). Antibiotics were excluded in this study since they were expected to have the wrong mode of action for fish. The problematic issue with antibiotics that a study performed by VGR (2008) focused on was the risk of development of resistant bacteria and not on specific effects for fish.

In VGR (2008), river PECs were derived by correcting MECs in WWTPs' effluent according to how much the effluent was diluted in the river . These PECs were then compared to PNEC values for each pharmaceutical. The risk quotient of MEC to PNEC for several pharmaceuticals indicated that the use of these substances posed a medium to high risk for adverse environmental effects. The study concluded that approx. 20 pharmaceuticals are present in recipients in the Västra Götaland county, more precisely recipients in Göteborg, Skövde and Borås, in such concentrations that adverse effects on the environment cannot be excluded. All but three of these 20 pharmaceuticals were selected for search for substance data in this study (Table 2). The three antibiotics ciprofloxacin, azithromycin and trimethoprim were excluded based on the same reason for why clarithromycine was excluded.

The study by VGR (2008) also included a section referring to a report by SEPA (2008) about known effects of pharmaceutical residues in the environment. Nine pharmaceuticals with proven effects on fish were described in this section, and these were also included in the search for substance data (Table 2).

Further, the pharmaceutical substances diclofenac, propranolol, carbamazepine and ethinylestradiol were, in the study by Westerdahl (2009), identified to possibly cause adverse effects to the aquatic environment. Therefore, these pharmaceuticals were also included in the search for substance data.

In total, 33 substances were initially selected to include in the search for substance data (Table 2).

Table 2: Substances that were included in the search for substance data with CAS-numbers, therapeutic groups and motivation of including them in the search for substance data.

Substance	CAS-number	Therapeutic group	Motivation
Citalopram	59729-33-8	antidepressant	a)
Flupentixol	2709-56-0	anti-psychotic drug	a)
Irbesartan	138402-11-6	hypertension drug	a)
Buprenorphine	52485-79-7	opioid	a)
Meclozine	569-65-3	anti-histamine	a)
Alprazolam	28981-97-7	treat anxiety disorders and panic disorder	b)
Bupropion	34911-55-2	antidepressant	b)
Clemastine	15686-51-8	antihistamines	b)
Diclofenac	15307-86-5	non-steroidal and anti-inflammatory drug (NSAID)	b), c) and d)
Haloperidol	52-86-8	antipsychotic	b)
Loperamide	53179-11-6	to control diarrhoea	b)
Sertraline	79617-96-2	antidepressant	b)
Tramadol	27203-92-5	analgesic	b) and c)
Verapamil	52-53-9	treatment of high blood pressure/chest pain	b)
Cetirizine	83881-51-0	remedy for allergy	c)
Oxazepam	604-75-1	sedative	c)
Diazepam	439-14-5	sedative	c)
Carbamazepine	298-46-4	antiepileptic	c) and d)
Clozapine	5786-21-0	agents for schizophrenia	c)
Dextropropoxyphene	469-62-5	analgesic	c)
Paracetamol (Acetaminophen)	103-90-2	analgesic	c)
Propranolol	525-66-6	anti-hypertensive	c) and d)
Hydrochlorothiazide	58-93-5	anti-hypertensive	c)
Isosorbide mononitrate	16051-77-7	agents for angina	c)
Warfarin	81-81-2	anticoagulant	c)
Ethinylestradiol	57-63-6	estrogen	c) and d)
Estradiol	50-28-2	estrogen	c)
Estriol	50-27-1	estrogen	c)
Estrone	53-16-7	estrogen	c) and d)
Ibuprofen	15687-27-1	anti-inflammatory	d)
Metoprolol	51384-51-1	anti-hypertensive	d)
Gemfibrozil	25812-30-0	blood-lipid-regulating	d)
Fluoxetin	54910-89-3	antidepressant	d)

a) Measured at levels expected to cause pharmacological effects in fish (Fick et al., 2011).
b) Measured close to levels expected to cause pharmacological effects in fish (Fick et al., 2011).
c) High to medium risk for environmental effects (VGR, 2008).
d) Pharmaceuticals with proven effects on fish (VGR, 2008; SEPA, 2008).

Searching for substance data

The selection of pharmaceuticals and the search for substance data was an iterative process. Due to limited available substance data it was impossible to include all the selected

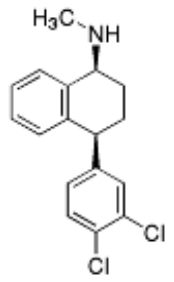
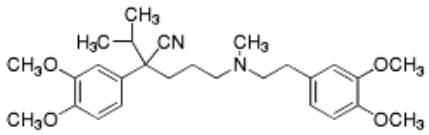
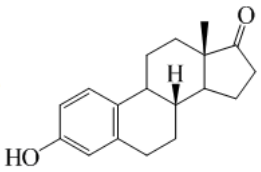
pharmaceuticals (Table 2) in the study, especially toxicity data for the chosen endpoints, *Salmo salar* and *Salmo trutta*, were difficult to obtain.

Stressor selection

Data for all four substance input parameters required in GREAT-ER were found for 12 of the 33 pharmaceutical substances listed in Table 2. These 12 pharmaceuticals were selected as stressors in this study (Table 3). The input data for the selected stressors are presented in section 3.3 and 3.4.

Table 3: Selected stressors, pharmaceuticals, to study with their CAS-number, chemical structure and therapeutic group.

Substance	CAS-number	Chemical structure	Therapeutic group
---	---		
Diclofenac	15307-86-5		anti-inflammatory
Propranolol	525-66-6		anti-hypertensive
Carbamazepine	298-46-4		antiepileptic
Ethinylestradiol	57-63-6		estrogen
Ibuprofen	15687-27-1		anti-inflammatory
Metoprolol	51384-51-1		anti-hypertensive
Gemfibrozil	25812-30-0		blood-lipid-regulating
Estradiol	50-28-2		estrogen
Paracetamol (Acetaminophen)	103-90-2		analgesic

Sertraline	79617-96-2		anti-depressant
Verapamil	52-53-9		treatment of high blood pressure and chest pain
Estrone	53-16-7		estrogen

3.3 Exposure assessment

In the exposure assessment, PECs were calculated by using the GREAT-ER model. This section gives a general description of the model, how the studied catchment area of the Göta Älv river was developed for GREAT-ER, the derivation of input data to the model, and finally descriptions of the implementation of the catchment into GREAT-ER and of how the results in the model can be presented are given.

3.3.1 General description of the GREAT-ER model

GREAT-ER uses four deterministic chemical fate models to relate consumption of chemicals to exposure in the catchment. These four models, which all were included in this study, are the emission model, sewer model, WWTP model and the river model. GREAT-ER also applies a stochastic approach using Monte Carlo simulation in order to account for spatial and temporal variability and uncertainties of the parameters that constitute the input to the model (GREAT-ER, 2014). Monte Carlo analysis implies that a problem is numerically solved, so that the equations describing the problem are solved many times, based on some random input variables described by statistical distributions. In this way an estimation of the probabilities of different outcomes is provided (Burgman, 2005). The number of times that the deterministic model equations are solved is called the number of Monte Carlo shots in GREAT-ER and was chosen to be 1 000 in this study. Input parameters that can be described as distributions in the model are for example R_{WWTP} and river flow data. However, due to limited availability of data, only river flow data were described as distributions in this study. The utilization of Monte Carlo simulation in the GREAT-ER model implies that the resulting PECs are given as distributions of concentrations (Wagner and Koorman, 2011). The model uses both a Geographical Information System (GIS) and chemical fate models in combination and is therefore able to provide a visualization of the PECs in the studied river in colour-coded maps (Cefic-LRI, 2014).

The development of the most current version of the software; GREAT-ER 3.0 Desktop from 2011 was done by the European Chemical Industry Council – the Long-range Research

Initiative (CEFIC-LRI) and Intevation GmbH. The original GREAT-ER 1.0 model was released in 1999 (Cefic-LRI, 2014).

3.3.2 Complexity modes

The number of input parameters that are needed in the GREAT-ER model depend on which of the three possible complexity modes for the chemical fate models that are chosen. The chemical fate models that are included in GREAT-ER are the emission model, the sewer model, WWTP model and the river model. The number of parameters that needs to be specified increase with the choice of a higher complexity mode for all the chemical fate models except for the emission model for which no increased complexity is introduced (Boeije, 1999).

The differences between the complexity modes 1, 2 and 3 that can be chosen for the sewer, WWTP and river models are summarized based on Boeije (1999) in Table 4. Complexity mode 1 was used in this study because of limitations in the available information regarding in-sewer removal, specific treatment steps of the studied WWTPs and regarding details for the in-stream removal of pharmaceuticals. The equations and parameters that are needed in GREAT-ER when complexity mode number 1 is used, for all the chemical fate models, are described in section 3.3.3. The data that is required in the creation of a catchment for GREAT-ER is described in section 3.3.8.

Table 4: Description of the differences between the complexity modes 1, 2 and 3 for the chemical fate models; sewer, WWTP and river in the GREAT-ER model based on Boeije (1999).

Complexity mode	Chemical fate model		
	Sewer	WWTP	River
1	No in-sewer removal	Fixed removal efficiency	First-order in stream removal, a fixed rate coefficient is assumed
2	In-sewer removal is assumed to be a fixed percentage	Mechanistic mathematical models and fixed values for removal are used for different treatment steps in the WWTP	First-order in stream removal, the rate coefficient is calculated with a formula that includes separate values for degradation, sedimentation and volatilization
3	As in complexity mode 2	As in complexity mode 2	First-order in stream removal with correction for solubility, the rate coefficient is calculated in more detail for the different sub-processes of degradation, sedimentation and volatilization than in complexity mode 2

3.3.3 Complexity mode 1

The model equations and parameters for GREAT-ER and complexity mode 1 that are described in this section are based on the Technical description of the GREAT-ER model version 1.0 and its chemical fate models (Boeije, 1999). This technical description is also valid for the GREAT-ER model version 3.0, which was used in this study. The input parameters that are required in GREAT-ER for complexity mode 1 are described with their symbol and unit in Table 5. Some of the parameters are calculated using equations [6] to [9].

In the emission model, the chemical mass flux (Φ) in g/s and the volumetric flux (Q) in m^3/s for domestic emissions are calculated using equations [6] and [7] respectively.

$$\Phi = \left(M \cdot \frac{1000}{365 \cdot 24 \cdot 3600}\right) \cdot Pop \quad [6]$$

$$Q = \left(W \cdot \frac{1}{1000 \cdot 24 \cdot 3600}\right) \cdot Pop \quad [7]$$

Where M is the consumed pharmaceuticals that enter the WWTP, Pop is the population connected to the WWTP and W is the water consumption per capita. Other emissions, non-domestic and run-off, can be entered into the GREAT-ER model separately.

The sewer model is not used for complexity mode 1. The parameter for the in-sewer removal (R_{SEWER}) is set to zero in this complexity mode. A fixed chemical removal efficiency (R_{WWTP}) is assumed for the WWTP model in complexity mode 1. In the river model, the first-order in-stream removal, that describes the chemical elimination in the river, are denoted (R_{RIVER}) and calculated with equation [8].

$$R_{RIVER} = 1 - e^{-HRT \cdot k} \quad [8]$$

A fixed rate coefficient (k) is assumed and the hydraulic residence time or travel time (HRT) is calculated using equation [9].

$$HRT = L/(v \cdot 3600) \quad [9]$$

Where L is the stretch length and v is the flow velocity.

Table 5: Summary of the input parameters needed in GREAT-ER when complexity mode 1 is used for all chemical fate models.

Parameter	Symbol	Unit
Emission model		
Chemical mass flux	Φ	g/s
Volumetric flux	Q	m^3/s
Consumption of chemicals, the quantity that enters the WWTP	M	kg/(capita*year)
Population connected to the WWTP	Pop	Capita
Per capita water consumption	W	L/(capita*day)
Sewer model		
Chemical removal in the sewer (set to be zero)	R_{SEWER}	-
WWTP model		
Chemical removal efficiency in the WWTP	R_{WWTP}	-
River model		
Chemical removal in the river	R_{RIVER}	-
Chemical in-stream removal rate	k	h^{-1}
Hydraulic residence, travel, time	HRT	h
Stretch length	L	m
Flow velocity	v	m/s

In addition to these parameters, another parameter called the offset concentration, that is an environmental background concentration, can be specified in GREAT-ER. There can be other sources of pharmaceuticals upstream the studied part of the Göta Älv river, implying that there are some background concentrations. However, the offset concentration was excluded in this study and thus it was assumed that there are no natural background concentrations of pharmaceuticals. This is contrary to metals, for which there are natural background

concentrations (Westerdahl, 2009). PNECs can also be specified in GREAT-ER and is required if RQs are to be calculated, see section 3.4.1.

The user must specify some of the parameters that are described in this section as input data for GREAT-ER. Other parameters are calculated in the program based on the input data. The data that need to be specified for GREAT-ER are summarized in Figure 6. This input data can be divided into two groups; substance data and catchment data. The catchment data can be divided further into three subgroups; river structure data, flow data and discharge site data (Figure 6).

The procedure of gathering information regarding required substance parameters for the exposure modelling in GREAT-ER is described in the following sections for R_{WWTP}, M and k. The substance data parameter PNEC is described in the effect assessment step in section 3.4. The catchment data is described in section 3.3.8.

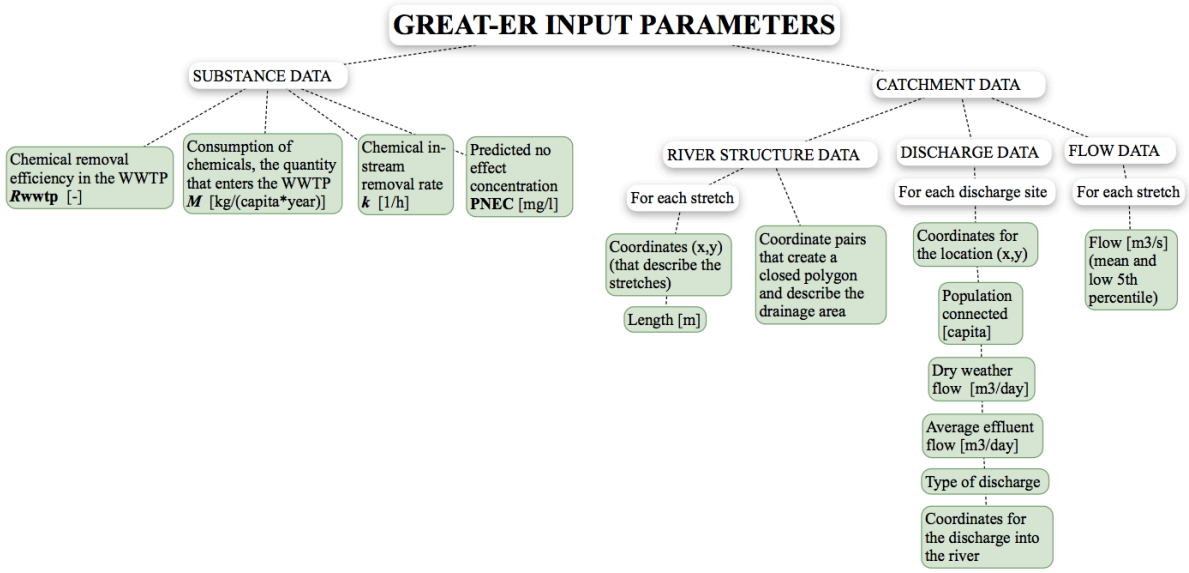


Figure 6: The input parameters that are needed for GREAT-ER when complexity mode 1 is used.

3.3.4 Average removal efficiency - R_{WWTP}

The average removal efficiency of pharmaceuticals in the WWTPs (R_{WWTP}) could not be found specifically for the WWTPs that are situated in the studied area of the Göta Älv river. Instead, R_{WWTP} values were obtained from other WWTPs in Sweden from Fick et al. (2011), VGR (2008) and SEPA (2008). Examples of WWTPs included in these studies are Rya in Göteborg, Gässlösa in Borås, Stadskvarn in Skövde, Henriksdal in Stockholm, Ön in Umeå and Kungsäng in Uppsala. The WWTPs included in these studies generally have a lot more people connected than the WWTPs included in this study.

The average removal efficiencies found in the studies by Fick et al. (2011), VGR (2008) and SEPA (2008) are presented in Table 6. The R_{WWTP} for some pharmaceuticals is stated to be quite different between the reports. Therefore, the mean of the reported average removal efficiencies were calculated and used as the input R_{WWTP} in GREAT-ER (Table 6).

Table 6: Average removal efficiencies of pharmaceuticals in WWTPs from Fick et al. (2011), VGR (2008) and SEPA (2008). R_{WWTP} is the calculated mean of the average removal efficiencies from the different studies. In GREAT-ER, R_{WWTP} has to be written as a number between zero and one. The same applies for example when R_{WWTP} is used in calculations with equations [11] and [12].

Substance	Average removal efficiency reported [%]	Reference	R_{WWTP} [%]
Diclofenac	28	Fick et al. (2011)	18
	11	SEPA (2008)	
	15	VGR (2008)	
Propranolol	-41	VGR (2008)	-33*
	-25	SEPA (2008)	
Carbamazepine	-3	IVL (2011)	-12*
	-40	SEPA (2008)	
	6.7	VGR (2008)	
Ethinylestradiol	>42	SEPA (2008)	42
Ibuprofen	71	IVL (2011)	76
	>85	SEPA (2008)	
	73	VGR (2008)	
Metoprolol	31	IVL (2011)	-5.5*
	-24	SEPA (2008)	
	-24	VGR (2008)	
Gemfibrozil	21	VGR (2008)	21
Estradiol	>72	SEPA (2008)	72
Paracetamol (Acetaminophen)	100	IVL (2011)	98
	96	VGR (2008)	
Sertraline	71	IVL (2011)	57
	18	SEPA (2008)	
	81	VGR (2008)	
Verapamil	26	IVL (2011)	26
Estrone	-39	VGR (2008)	-39*

* Since these values for R_{WWTP} are negative, the R_{WWTP} had to be set to zero in GREAT-ER while the values for M had to be corrected to account for that for these pharmaceuticals.

The R_{WWTP} values for propranolol, carbamazepine, metoprolol and estrone in Table 6 are negative and studies considering removal efficiencies for WWTPs often encounters negative values (Fick et al., 2011). A negative value for R_{WWTP} can to some extent be explained by the fact that some pharmaceuticals are excreted from the human body as metabolites, for example as glucuronide conjugates (Fick et al., 2011; VGR, 2008). Then the conjugate is converted back to the original compounds when it is decomposed in the WWTP so that higher concentrations of the pharmaceutical are found in the effluent compared to the influent. Another explanation of negative values for R_{WWTP} is the larger difficulties coupled to measurements of pharmaceutical concentrations in waste water compared to treated water (VGR, 2008). The way that the samples are analysed can also affect the measurement results. A negative value for R_{WWTP} can also imply that the pharmaceutical is formed as a metabolite from the degradation of another pharmaceutical in the WWTP. An example is estrone that is formed as a metabolite from the degradation of ethinylestradiol (Lienert et al., 2007).

In GREAT-ER, R_{WWTP} has to by definition be between zero and one. This was necessary to take into consideration in section 3.3.5 and section 3.3.6 in the calculations of *M* for propranolol, carbamazepine, metoprolol and estrone.

3.3.5 Backward calculation of *M*

The pharmaceutical consumption (*M*) in kg/(capita*year) is a parameter in GREAT-ER of the quantity of pharmaceuticals that enters the WWTP. *M* in this study, was derived by backward calculation from flow-related mean values of measured levels of pharmaceuticals in WWTP influents and effluents for different Swedish WWTPs in the studies by VG (2008) and Fick et al. (2011). The flow-related mean values for pharmaceuticals in WWTP influents (FMI_i) were multiplied with the total annual flow through the WWTPs ($F_{tot, annual}$) and divided by the number of people connected to the WWTP (Pop) (equation [10]).

$$M_{Backward\ calc,i} = (FMI_i \cdot 10^{-12} \cdot F_{tot,annual} \cdot 1000)/Pop \quad [10]$$

When flow-related mean values for pharmaceuticals in WWTP effluents were available, the average removal efficiency for each pharmaceutical in WWTPs ($R_{WWTP,i}$) was also used to calculate *M* (equation [11]).

$$M_{Backward\ calc,i} = (\frac{FME_i}{1-R_{WWTP,i}} \cdot 10^{-12} \cdot F_{tot,annual} \cdot 1000)/Pop \quad [11]$$

The parameters in equation [10] and [11] are described in Table 7.

Table 7: Description of the parameters in equation [10] and [11] with their symbol and unit.

Parameter	Symbol	Unit
Consumption of pharmaceutical *i*, quantity entering the WWTP, derived from backward calculation	$M_{Backward\ calc,i}$	kg/(capita*year)
Flow-related mean value for measured levels in WWTP influent of pharmaceutical *i*	FMI_i	ng/l
Flow-related mean value for measured levels in WWTP effluent of pharmaceutical *i*	FME_i	ng/l
Total annual flow through the WWTP	$F_{tot,annual}$	m^3/year
Population connected to the WWTP	Pop	capita
Average removal efficiency in the WWTP for pharmaceutical *i*	$R_{WWTP,i}$	-

Flow-related mean values for measured levels of pharmaceuticals in the effluent from Rya, Stadskvarn and Gässlösa WWTP in Göteborg, Skövde and Borås respectively were available in VGR (2008) for all pharmaceuticals, except for verapamil (Table 8).

Table 8: Flow-related mean values of measured pharmaceutical levels in effluents from Rya, Stadskvarn and gässlösa WWTP (FME_i) measured in 2008, (VGR, 2008) . For values given as less than a specific number in an open interval the specific number was used as the value for FME_i.

	Flow-related mean of measured levels in effluent, FME_i [ng/l]		
Substance	**Rya WWTP, Göteborg**	**Stadskvarn WWTP, Skövde**	**Gässlösa WWTP, Borås**
Diclofenac	140	280	160
Propranolol	38	76	100
Carbamazepine	350	1 100	920
Ethinylestradiol	< 1	< 1	< 1
Ibuprofen	730	150	340
Metoprolol	590	1 070	1 320
Gemfibrozil	150	390	110
Estradiol	< 1	< 0.7	< 0.8
Paracetamol (Acetaminophen)	1 220	49	190
Sertraline	9.9	< 6.4	< 10
Estrone	14	2.3	8.5

A flow-related mean for measured levels in influent (FMI_i) for verapamil of 50 ng/l was obtained from Fick et al. (2011). In the study by Fick et al. (2011), the average concentration of verapamil was presented based on measurements from 2010 at the influent of four different WWTPs. These four WWTPs were Stadskvarn, Henriksdal, Ön and Kungsäng WWTPs situated in Skövde, Stockholm, Umeå and Uppsala respectively.

The total annual flow through the WWTPs together with the number of people connected to the WWTPs, for which flow-related mean values for measured levels of pharmaceuticals were found in influent and effluent, are presented in Table 9. The information was obtained from the environmental reports for the WWTPs for the years 2008 and 2010. These years were chosen since they were the years when the measurements in VGR (2008) and Fick et al. (2011) were performed.

Table 9: The total annual flow and the number of people connected to the WWTPs for the years when the measurements were made in VGR (2008) and Fick et al. (2011).

WWTP	**Total annual flow [m3/year]**	**Population connected [capita]**	**Reference**
Rya WWTP, Göteborg	136 500 000	640 303	Miljörapport (2009)
Stadskvarn WWTP, Skövde	4 907 944	39 500	Miljörapport (2008a)
Gässlösa WWTP, Borås	16 560 364	81 544	Miljörapport (2008b)
Stadskvarn WWTP, Skövde	4 784 769	39 500	Miljörapport (2010b)
Henriksdal WWTP, Stockholm	91 800 000	752 700	Miljörapport (2010c)
Ön WWTP, Umeå	12 490 850	92 118	Miljörapport (2010d)
Kungsäng WWTP, Uppsala	19 288 390	160 200	Miljörapport (2010a)

The flow-related mean value for measured levels of verapamil was given as an average calculated from measurements in 2010 in influents from the four Swedish WWTPs Stadskvarn, Henriksdal, Ön and Kungsäng (Fick et al., 2011). The average total annual flow

and average connected population for these four WWTPs were calculated to be 32 091 002 m^3/year and 261 130 people connected (Table 9).

In Table 10, the removal efficiency of pharmaceuticals in Rya WWTP is presented. Data on removal efficiencies for some pharmaceuticals were not available as well as removal efficiencies for the WWTPs Stadskvarn and Gässlösa. In these cases the average removal efficiencies in Table 6 in section 3.3.4 were used.

Table 10: Removal efficiencies for some selected pharmaceuticals in Rya WWTP VG (2008).

	R_{WWTP} [%]
Substance	**Göteborg, Rya WWTP**
Diclofenac	15
Propranolol	-41
Carbamazepine	6.7
Ethinylestradiol	Not available
Ibuprofen	73
Metoprolol	-24
Gemfibrozil	21
Estradiol	Not available
Paracetamol (Acetaminophen)	96
Sertraline	81
Verapamil	Not available
Estrone	-39

The *M*-values for propranolol, carbamazepine, metoprolol and estrone had to be corrected since R_{WWTP} has to by definition be between zero and one in GREAT-ER. The amounts of these pharmaceuticals leaving the WWTP ($M_{out,i}$) were therefore calculated according to equation [12]. This value was then used as the input value for *M* in GREAT-ER and the value for R_{WWTP} was set to zero. The parameters in equation [12] are described in Table 11.

$$M_{out,i} = M_i \cdot (1 - R_{WWTP,i}) \quad [12]$$

Table 11: Description of the parameters in equation [12].

Parameter	Symbol	Unit
Consumption of pharmaceutical *i*, quantity leaving the WWTP	$M_{out,i}$	kg/(capita*year)
Consumption of pharmaceutical *i*, quantity entering the WWTP	M_i	kg/(capita*year)
Average removal efficiency in the WWTP of pharmaceutical *i*	$R_{WWTP,i}$	-

More specifically, M_i is equal to $M_{Backward\ calc,i}$ when backward calculation is used to derive *M*.

The values for *M* based on backward calculation for all the selected pharmaceuticals (Table 3) are presented in Table 12 were the values for *M* for pharmaceuticals with negative values for R_{WWTP} has been corrected.

Table 12: Average *M* obtained with backward calculation.

Substance	Average $M_{Backward\ calc}$ [kg/(capita*year)]
Diclofenac	3.9E-05
Propranolol	1.3E-05*
Carbamazepine	1.4E-04*
Ethinylestradiol	3.1E-07
Ibuprofen	3.2E-04
Metoprolol	1.7E-04*
Gemfibrozil	4.4E-05
Estradiol	5.5E-07
Paracetamol (Acetaminophen)	2.6E-03
Sertraline	5.8E-06
Verapamil	6.1E-06
Estrone	1.6E-06*

* Corrected due to the requirement in GREAT-ER of values for R_{WWTP} between zero and one.

3.3.6 Forward calculation of *M*

Forward calculation of *M* is perhaps a more conventional way of determining *M* alternative to backward calculation. When *M* is obtained by forward calculation ($M_{Forward,calc}$), the fate of the pharmaceuticals from the purchase to the excretions of them finally reaching the WWTP, is considered. For further information, see the conceptual model in section 3.2.1. Due to difficulties in finding data regarding sale statistics that could be converted to the right unit of kg per capita and year values for *M* obtained with forward calculation was not used in this study. However, the procedure to obtain *M* by forward calculation is described in this section since it is a conventional option and was part of this study until it was found out that there was not enough data to calculate M in this way. Values for *M* for the pharmaceuticals for which was possible to obtain with forward calculation are also presented.

Sale statistics for pharmaceuticals in Sweden, and specifically in the County of Västra Götaland were required. Other data needed for the forward calculation of *M* are the fraction of the consumed pharmaceutical that is excreted, that is the fraction that is not metabolized in the human body. A strategy for converting the sale statistics, generally given in the measurement unit of Defined Daily Doses (DDDs) per thousand capita and year, into kg per capita and year is also required and was done using the ATC-DDD classification system.

ATC-DDD classification system

The World Health Organization (WHO) recommends the ATC-DDD classification system for drug utilization research. The Anatomical Therapeutic Chemical (ATC) classification system and DDDs are widely used internationally (WHOCC, 2013). In the ATC-DDD classification system, each pharmaceutical is given a specific ATC code based on the main therapeutic route for the main ingredient and for each route of administration. Then, a DDD in for example the unit of gram can be assigned to each route of administration for the ATC codes. DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHOCC, 2013).

Sale statistics for pharmaceuticals

A strategy was developed to be able to convert sale statistics into kg per capita and year (Figure 7), that is the required input unit for *M* in GREAT-ER. Figure 7 shows that it is not only critical that sale statistics can be obtained for pharmaceuticals as well as their ATC codes. If the ATC codes do not have any assigned DDDs, the information cannot be converted into the right format of kg per capita and year that is required by GREAT-ER.

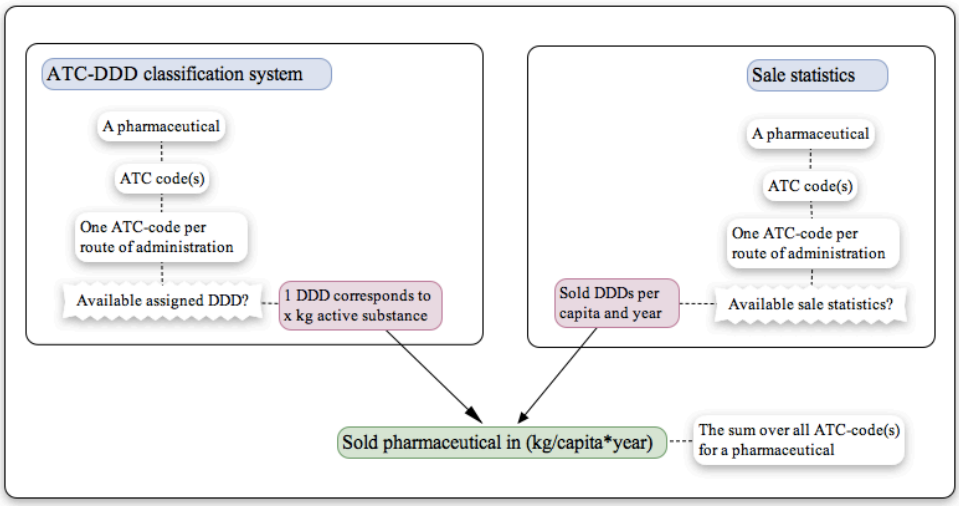


Figure 7: Strategy for converting sale statistics in DDD/(capita*year) into kg/(capita*year).

Existing ATC codes with assigned DDDs for each pharmaceutical was searched for with name and CAS-number for all the selected pharmaceuticals (Table 3) on the web page of the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC, 2014). For some pharmaceuticals there existed several ATC codes, some of them for combination products. However, many of the ATC codes did not have any assigned DDD specifying how much kg active substance that one DDD corresponds to. Thus possible DDDs from sale statistics for these ATC codes could not be converted into kg active pharmaceutical substance.

Sale statistics were obtained in the form of sold DDDs per thousand inhabitants for Sweden in the county of Västra Götaland for the years 2009-2013 from the Swedish eHealth Agency (Rehnberg, 2014). Sale statistics were given for all the selected pharmaceuticals except for ethinylestradiol and estrone. The sale statistics were then converted into kg per capita and year using the ATC-DDD classification system and assigned DDD values (Appendix 7.1).

The reason why sale statistics for 2009-2013 in Västra Götaland could not be obtained for ethinylestradiol and estrone was that none of these pharmaceuticals had been sold during this period. That is no ethinylestradiol or estrone with ATC codes for which there were assigned DDDs available on the WHOCC webpage (WHOCC, 2014) had been sold during this period. Ethinylestradiol are sold in Sweden, but then in combination with other pharmaceuticals (Rehnberg, 2014). The problem is that there are no assigned DDDs for these combination products. Estrone, on the other hand, is very unusual in pharmaceuticals. For example, there exist no approved pharmaceuticals with estrone in Sweden according to Rehnberg (2014). However, estrone is excreted naturally from humans (Khanal et al., 2006) and it is also a metabolite of ethinylestradiol that is another estrogen (Lienert et al., 2007). This makes it reasonable to include estrone when pharmaceutical residues are studied in waters such as in the study by VGR (2008), but difficult to derive *M* for estrone using forward calculation. This was an important reason for why backward calculation of *M* was chosen instead. Another important reason was that a lot of uncertainties, in for example the amount of the sold

pharmaceuticals that actually are consumed and in the excretion of pharmaceuticals, are avoided by using backward calculation.

Fraction not metabolized in the human body - f_{nm}

The fraction of a pharmaceutical that is not metabolized in the human body but excreted (f_{nm}) was found in the studies by Jjemba (2006), Johnson et al. (2013), Ferrari et al. (2004), Calisto and Esteves (2009) and Lienert et al. (2007). Values for f_{nm} were found for all selected pharmaceuticals (Appendix 7.1) except for estrone. Excretion of estrone from pharmaceutical consumption was not found, most certainly because estrone is very unusual in pharmaceuticals (Rehnberg, 2014).

The average value for *M* obtained with forward calculation was given from the total sold kg/capita*year in the Västra Götaland county for the years 2009-2013 and from calculated average f_{nm} values (Appendix 7.1). The average *M* is given for all selected pharmaceuticals in Table 13, except for ethinylestradiol and estrone for which data were missing. In Table 13, the value for *M* has been corrected for propranolol, carbamazepine and metoprolol according to section 3.3.5. All the information that was required to obtain *M* with forward calculation is given in Appendix 7.1.

Table 13: Average *M* for 2009-2013 obtained with forward calculation.

Substance	Average $M_{Forward,calc}$ [kg/(capita*year)]
Diclofenac	6.8E-05
Propranolol	4.9E-06*
Carbamazepine	1.3E-05*
Ethinylestradiol	No data
Ibuprofen	1.4E-3
Metoprolol	1.6E-4*
Gemfibrozil	1.2E-05
Estradiol	1.0E-07
Paracetamol (Acetaminophen)	1.8E-3
Sertraline	8.2E-07
Verapamil	3.7E-06
Estrone	No data

* Corrected due to the requirement in GREAT-ER of values for R_{WWTP} between zero and one.

The differences between *M* obtained with backward and forward calculation are discussed in section 4.1.1.

3.3.7 In-stream removal rate - *k*

The in-stream removal rate of chemicals (*k*) is in GREAT-ER described as a function of the removal of chemicals in water due to degradation (k_{deg}), sedimentation (k_{sed}) and volatilization (k_{vol}) (Boeije, 1999), see equation [13]. f_s and f_d in equation [13] are the sorbed chemical fraction and the dissolved chemical fraction respectively. All the parameters that are presented in this section are summarized in Table 14. In this study, the chemicals are the pharmaceuticals that were selected in Table 3.

$$k = k_{deg} + f_s \cdot k_{sed} + f_d \cdot k_{vol} \quad [13]$$

If it can be assumed that $k_{sed} \approx 0$ and $k_{vol} \approx 0$ then the expression for k in equation [13] would become $k \approx k_{deg}$. This would not only simplify the expression of equation [13], but also the search for information regarding the in-stream removal. Removal rates of pharmaceuticals in the aquatic environment that in general can be found in the literature are half lives. That is the time it takes for a chemical to degrade to half of its initial concentration.

In this study, k_{sed} was assumed to be zero in the Göta Älv river. This assumption was founded on an article by Göransson et al. (2013) stating that there is almost no sedimentation in the river. In this article, turbidity that is used as a measure of water quality was studied in the Göta Älv river.

Volatilization from water surfaces, according to the PubChem Compound database (PubChem, 2014), is not expected to be an important environmental fate process for diclofenac, carbamazepine, ethinylestradiol, metoprolol, ibuprofen, gemfibrozil, estradiol, paracetamol or estrone. For all of these pharmaceuticals, except for diclofenac and gemfibrozil, this expectation was based on their Henry's law constant. Diclofenac and gemfibrozil were not expected to volatilize from water surfaces since they will exist almost entirely in their anion form in pH values from 5 to 9. Volatilization is an important removal process when the air-water partition coefficient, that is Henry's law constant, is high (Rand, 1995). According to Rand (1995), a chemical with a Henry's law constant $< 3 \cdot 10^{-7}$ atm m^3/mol has a lower volatilization potential than water. The Henry's law constant for the other selected pharmaceuticals propranolol and verapamil were 7.98E-13 and 8.79E-15 atm m^3/mol respectively (NLM, 2014) and 5.1E-8 atm m^3/mol for sertraline (PHYSPROP, 2014). The Henry's law constant for propranolol, verapamil and sertraline are smaller than the volatilization potential of water. Therefore, volatilization is not expected to be an important environmental fate process for these pharmaceuticals either. Based on these findings, k_{vol} was assumed to be zero for all the selected pharmaceuticals in this study.

If the half life for a pharmaceutical is known, while $k_{sed} \approx 0$ and $k_{vol} \approx 0$ then $k \approx k_{deg}$ can be calculated with equation [17] derived from equation [14].

$$C_x = C_{x0} \cdot e^{-k \cdot t} \quad [14]$$

At the time $t_{1/2}$, that is the half-life for a pharmaceutical:

$$C_x = \frac{1}{2} \cdot C_{x0} \quad [15]$$

Equation [14] and [15] leads to equation [16]:

$$\frac{1}{2} = e^{-k \cdot t_{1/2}} \quad [16]$$

This expression can then be re-written into:

$$k = \frac{\ln(2)}{t_{1/2}} \quad [17]$$

Table 14: Description of the parameters in equation [13] to [17].

Parameter	Symbol	Unit
In-stream removal rate of chemicals	k	h^{-1}
First order chemical degradation rate in the dissolved phase	k_{deg}	h^{-1}
First order net suspended solids settling rate	k_{sed}	h^{-1}
First order chemical volatilization rate	k_{vol}	h^{-1}
Sorbed chemical fraction	f_s	-
Dissolved chemical fraction	f_d	-
Concentration of chemical x	C_x	mol/dm^3
Initial concentration of chemical x	C_{x0}	mol/dm^3
Time	t	h
Half life, the time it takes for a chemical to degrade to half of its initial concentration	$t_{1/2}$	h

In Table 15, half lives in the aquatic environment, for the selected pharmaceuticals, found in the literature are presented as well *k* values calculated using equation [17]. An aquatic half life for verapamil was, however, not found in the literature. According to the experimental results of a study by Trautwein et al. (2008), verapamil is not readily biodegradable. In a photolytic destruction experiment, verapamil was degraded more slowly than another pharmaceutical, trimethoprim (Lunn et al., 1994). Trimethoprim on the other hand has been shown to be stable in seawater exposed to sunlight (PubChem, 2014). Based on this information, the aquatic half life for verapamil is assumed to be such a large value that the degradation of verapamil in the Göta Älv river is negligible. Therefore, the value for the aquatic half life for verapamil was set to 150 days, which is longer than for most of the other studied pharmaceuticals. It is also much longer than the time it takes for the water to travel from Vänern to Lärjeholm (Göransson et al., 2013), see section 2.2. Lärjeholm lies close to the point where Säveån reaches the Göta Älv river and therefore the travel time stated in Göransson et al. (2013) can be considered to be applicable for the studied area.

Table 15: Calculated in-stream removal rate of pharmaceuticals (*k*).

Substance	*k* [1/h]	Aquatic half life [days]	Reference
Diclofenac	0.0036	8	PubChem (2014)
Propranolol	0.036	(Given as *k*)	Alder et al. (2010)
Carbamazepine	0.00046	63	PubChem (2014)
	0.00076	38	PubChem (2014)
	0.00035	82	Lam et al. (2004)
	0.00052	(Average *k* based on found data)	
Ethinylestradiol	0.00167	17.3	Johnson et al. (2013)
	0.0017	17	Sumpter et al. (2006)
	0.00168	(Average *k* based on found data)	
Ibuprofen	0.0014	20	PubChem (2014)
Metoprolol	0.00079	(Given as *k*)	Alder et al. (2010)
Gemfibrozil	0.00024	119.5	Araujo et al. (2011)
Estradiol	0.013	2.3	Johnson et al. (2013)
	0.0096	3	Sumpter et al. (2006)
	0.011	(Average *k* based on found data)	
Paracetamol (Acetaminophen)	0.032	0.9	Lam et al. (2004)
Sertraline	0.0046	6.3	Lam et al. (2004)
Verapamil	0.00019	150 (assumed)	Trautwein et al. (2008), Lunn et al. (1994), PubChem (2014) and Göransson et al. (2013)
Estrone	0.0058	5	Sumpter et al. (2006)

3.3.8 The catchment of the Göta Älv river

The substance data for the selected stressors in section 3.2.2, together with a model of the river catchment must be implemented into GREAT-ER to be able to model the exposure of pharmaceuticals to fish in the Göta Älv river. This section explains the process of creating the catchment and presents the data that was required in order to describe it. The catchment data is divided into three different types of data that are described more thoroughly (Figure 6). These three types are the river structure data, discharge site data and flow data. In the end of this section the implementation of the catchment into GREAT-ER and the simulation results provided by GREAT-ER are explained briefly.

The catchment was developed by dividing the river into segments, that is stretches, and describing the flow in each stretch. The stretches connected to point sources (WWTPs) were specified and the WWTPs were described. Data needed to describe the stretches are river structure data, discharge site data and flow data, which are connected to each other and this must be considered in the development of the catchment. The development of the river structure or the division of the river into stretches was dependent on available flow data. At the same time, the segmentation is dependent on the discharge site data including information about the coordinates where the emissions from the WWTPs reach the river.

River structure data

The river structure data, used to construct a one-dimensional model of the river catchment, divides the river into stretches and describes the natural drainage area of the catchment. Coordinates for the river stretches and the length of these were obtained from the County

Administrative Board Webb-GIS application (Länsstyrelsen, 2014), which uses the SWEREF 99 TM coordinate system. Therefore, the coordinates were entered into the source files for GREAT-ER in the SWEREF 99 TM coordinate system format. The river structure data that needs to be defined in GREAT-ER are coordinates describing the stretches and the length of the stretches in meters. A number of coordinate pairs, at least two, were used to describe a stretch. The endpoint of a stretch and the starting point of the following stretch must be identical for the stretches to be connected. The coordinates describing the river stretches must be entered in a downstream direction. Coordinates forming a closed polygon, which objective is to provide an impression of the natural drainage area, are also required. However, these coordinates can be chosen so that a proper visualization of the natural drainage area is included or not. In this study, the visualization of the natural drainage area of the Göta Älv river was not included and cannot be seen in Figure 8.

In order to be able to divide the river into stretches and hence select the appropriate coordinates to describe the stretches, data such as the water flow in specific points, the length of the stretches and the discharge site coordinates for the WWTP effluent into the river were needed. The dependence of the river structure data on the discharge site data is due to GREAT-ER that is constructed so that the effluent from a discharge site is emitted into the river at the starting point of the river stretch to which it is connected to. Coordinates were therefore primarily chosen based on for which points measured or modelled flow data were available and where the WWTPs were located. Otherwise, points in or close to the middle of the width of the river were chosen. Since the model of the catchment is one-dimensional the width of the river cannot be explained. The coordinates where chosen so that all the stretches in the catchment had approx. the same length, that is approx. one km each. The decision to have stretches of approximately the same length was made so that results could be more easily interpreted.

Flow data of tributaries to the river from SMHIs VattenWebb (SMHI, 2014) were included if existing, but only one km of the part closest to the river. Thus, tributary flows for which flow data could not be obtained were not included in the catchment in this study. Another simplification that was made in the development of the catchment was that WWTPs or points with flow data for tributaries located close to each other, close in relation to the one km length of the stretches, were assumed to have the same outlet point.

In total, the river was divided into 115 stretches from the outflow of Vänern to the point where Säveån reaches the river.

Discharge site data

There are eight WWTPs, discharge sites, situated along the studied part of the Göta Älv river. These are, mentioned in the order of their position from the outflow of Vänern and in downstream direction; Vänersborg, Trollhättan, Hjärtum, Lilla Edet, Lödöse, Nygård, Älvängen and Diseröd WWTPs. There is a WWTP located in Gothenburg; Rya WWTP to which wastewater is led from the surrounding municipalities, but this WWTP is not included in this study since it is situated outside the studied area. In Table 16, the studied WWTPs are listed together with their municipality and authority of supervision.

Table 16: Discharge sites situated along the Göta Älv river with their municipality and authority of supervision.

WWTP	Municipality	Authority of supervision
Vänersborg, Holmängen	Vänersborg	Municipality of Vänersborg
Trollhättan, Arvidstorp	Trollhättan	County Administrative Board of Västra Götaland
Hjärtum	Lilla Edet	Municipality of Lilla Edet
Lilla Edet, Ellbo	Lilla Edet	County Administrative Board of Västra Götaland
Lödöse	Lilla Edet	Municipality of Lilla Edet
Nygård	Lilla Edet	Municipality of Lilla Edet
Älvängen	Ale	County Administrative Board of Västra Götaland
Diseröd	Kungälv	Municipality of Kungälv

The discharge site data for the eight WWTPs was obtained from environmental reports and annual reports for the year 2013 for each WWTP respectively. The environmental reports for Vänersborg WWTP (Miljörapport, 2013d), Trollhättan WWTP (Miljörapport, 2013c), Lilla Edet WWTP (Miljörapport, 2013b) and Älvängen WWTP (Miljörapport, 2013e) were supplied by the County Administrative Board of Västra Götaland. The municipality of Lilla Edet supplied the annual reports for Hjärtum WWTP (Årsrapport, 2013a), Lödöse WWTP (Årsrapport, 2013b) and Nygård WWTP (Årsrapport, 2013c). The municipality of Kungälv supplied the environmental report for Diseröd WWTP (Miljörapport, 2013a).

The input discharge site data that is needed for GREAT-ER are how many persons that are connected to each WWTP, the dry weather flow, the effluent flow and the type of discharge (Table 17). Required data are also the locations of the WWTPs (Table 18) and the coordinates for the positions where the WWTP effluents discharges into the river (Table 19).

Table 17: Parts of the discharge data; number of connected people to the WWTP, Dry weather flow, average effluent flow and the type of discharge obtained from environmental and annual reports for the WWTPs. PS stands for primary settler.

WWTP	People connected to the WWTP [capita]	Dry weather flow [m^3/day]	Effluent flow [m^3/day]	Type of discharge	Reference
Vänersborg, Holmängen	27 443	6 280	13 282	PS	Miljörapport (2013d)
Trollhättan, Arvidstorp	56 573	7 006	26 123	PS	Miljörapport (2013c)
Hjärtum	386	21	96	PS	Årsrapport (2013a)
Lilla Edet, Ellbo	5 759	700*	2 015	PS	Miljörapport (2013b)
Lödöse	1 311	107	434	PS	Årsrapport (2013b)
Nygård	415	32	78	PS	Årsrapport (2013c)
Älvängen	6 158	802	2 095	PS	Miljörapport (2013e)
Diseröd	1 200	110*	316	PS	Miljörapport (2013a)

* These values were estimated based on the relation between minimal flow and average effluent flow for other WWTPs.

The effluent flow in Table 17 is the average outflow from a WWTP. The dry weather flow was selected to be the average minimum flow out from the WWTPs. However, the minimum outflow was not available in the environmental report or annual report for Lilla Edet and

Diseröd WWTP. Therefore, the minimum outflow had to be estimated for these WWTPs. A dry weather flow fraction was derived by dividing the dry weather flow with the average effluent flow for all the other WWTPs, for which information was available about the minimum flow. After that, an average dry weather flow fraction was calculated to be 0.35. The calculated dry weather flows for Lilla Edet and Diseröd WWTP based on this fraction were 700 m^3/day and 110 m^3/day respectively.

The parameter "type of discharge" is only considered in higher complexity modes, modes 2 and 3 for the WWTP chemical fate model, and is then used to estimate R_{WWTP}. In this study, the type of discharge is not used since complexity mode 1 was utilized see section 3.3.2 and 3.3.3. However, the parameter must still be defined because it is compulsory in GREAT-ER. The type of discharge can be either primary settler (PS), activated sludge (AS), trickling filter (TF) or activated sludge/trickling filter (AS/TF) and represent different estimation methods for R_{WWTP} that are used in higher complexity modes. In this study, the type of discharge was just chosen to be PS.

In GREAT-ER, the coordinates for the discharge sites are included and thus the plants can be visualized. The coordinates of the discharge site describe the position of the actual plant and not the point at which emissions enter the river. In Table 18, the coordinates for the discharge sites are presented for the studied WWTPs.

Table 18: Parts of the discharge data; coordinates for the actual plant in the coordinate system of SWEREF 99 TM.

WWTP	Coordinates for the actual plant N x E	Reference
Vänersborg, Holmängen	6474302 x 344487	Miljörapport (2013d)
Trollhättan, Arvidstorp	6462586 x 339311	Miljörapport (2013c)
Hjärtum	6452173.990 x 330578.236	Åberg (2014)
Lilla Edet, Ellbo	6446148.43 x 330658.48	Länsstyrelsen (2014)
Lödöse	6435614.798 x 331673.180	Åberg (2014)
Nygård	6438243.864 x 335238.268	Åberg (2014)
Älvängen	6428164 x 329968	Miljörapport (2013e)
Diseröd	6424297 x 324384.781	Mårtensson (2014a)

The coordinates for the location of Hjärtum, Lödöse, Nygård and Diseröd WWTP were not available from the environmental and annual reports for these WWTPs. Therefore, these coordinates were instead received by Mr. Göran Åberg, municipality of Lilla Edet (Åberg, 2014), and Mr. Agne Mårtensson, municipality of Kungälv (Mårtensson, 2014a). However, the coordinates were given in the SWEREF 99 12 00 coordinate system and had to be transformed to the SWEREF 99 TM coordinate system. The transformation was done by using the Swedish Land Surveying's application for transforming between coordinate systems (Lantmäteriet, 2014). The coordinates for the location of Lilla Edet WWTP was obtained from the County Administrative Board of Västra Götaland Webb-GIS information map (Länsstyrelsen, 2014).

The discharge outlet point coordinates in Table 19 are the coordinates for the points where the treated wastewater from the WWTP and overflows at the WWTP enters the river. There can be three types of effluent of wastewater connected to a WWTP, that is treated wastewater at the WWTP, overflows at the WWTP and overflows from the main system and pumping

stations. In the case of all the WWTPs studied, the treated wastewater and overflows at the WWTP are discharged at the same place. Overflows at the main system and pumping stations for the WWTPs have not been included in this study. The reason for this is the combination of the in general multiple overflow outlet points in connection to the WWTPs and missing data for the exact location of these points. The possible effects on the concentration of pharmaceuticals in the river from neglecting overflows at main systems and pumping stations for the WWTPs are discussed in section 4.6.2.

Table 19: Part of the discharge data; coordinates in the SWEREF 99 TM coordinate system for outlet points for treated wastewater from the WWTPs and overflows at the WWTPs.

WWTP	Discharge outlet point coordinate N x E	Reference
Vänersborg, Holmängen	6474223.67 x 345523.93	Miljörapport (2013d)
Trollhättan, Arvidstorp	6462386 x 339324	Miljörapport (2013c)
Hjärtum	6452109.604 x 330675.463	Åberg (2014)
Lilla Edet, Ellbo	6446135.249 x 330534.626	Åberg (2014)
Lödöse	6435587.938 x 331601.920	Åberg (2014)
Nygård	6438198.689 x 335241.264	Åberg (2014)
Älvängen	6428319.48 x 329788.8	Sundberg (2014)
Diseröd	6424133.222 x 325821.180	Mårtensson (2014) and Miljörapport (2013a)

The coordinates for the point of discharge for the WWTP of Vänersborg was not available through the environmental report, but was estimated based on the information presented in the environmental report. However, the report only states that the emissions of both treated flows and overflows at the WWTP are discharged at the outflow of Vänern into the river of Göta Älv. Due to the uncertainty of the exact position of the WWTP discharge outlet point and the usage of a one-dimensional model, a coordinate for the point of discharge for the WWTP into the river was chosen to be in the middle of the width of the river. The position was chosen close to the WWTP, but downstream the bird preservation area, where the point of discharge was not expected to be located.

The coordinates for the point of discharge of both treated wastewater from the WWTP and overflows at the WWTP of Älvängen were also estimated. The point was estimated to be located in the middle of the width of the river and close to the WWTP. The assumption was based on a conversation with Sundberg (2014). For Diseröd WWTP, the point of discharge into Göta Älv is the same for treated wastewater from the WWTP and overflows at the WWTP. This information was found in the environmental report for the WWTP. However, the coordinate for the outlet point for Diseröd WWTP could not be found in the environmental report for the WWTP but was received from Mårtensson (2014). The discharge outlet point coordinates for Hjärtum, Lilla Edet, Lödöse, Nygård and Diseröd WWTP was given in SWEREF 99 12 00 and hence were transformed to the coordinate system SWEREF 99 TM using the Swedish Land Surveying's application(Lantmäteriet, 2014).

The treated fraction (*TF*) of the total annual discharged wastewater from each WWTP was entered into GREAT-ER, though this is not compulsory. The annual total flow through each WWTP and the total annual overflow at the WWTPs were found in the environmental reports for the respective WWTP (Table 20). Overflows at the WWTPs were mainly due to hydraulic

overloading but were in some cases caused by damages in the operation processes. In this study, it was assumed that the overflows at the WWTPs were not treated.

The data in Table 20 were used to calculate the *TF*. In the case of Hjärtum and Nygård WWTPs, there were no information available in their respective environmental reports regarding possible overflows at the WWTPs.

Table 20: Total annual flow through the WWTPs and overflow at the WWTPs.

WWTP	Total annual flow through the WWTP [m^3/year]	Total annual overflow at the WWTP [m^3/year]	Reference
Vänersborg, Holmängen	4 847 986	822	Miljörapport (2013d)
Trollhättan, Arvidstorp	9 542 923	767 138	Miljörapport (2013c)
Hjärtum	34 931	0	Årsrapport (2013a)
Lilla Edet, Ellbo	735 465	33 538	Miljörapport (2013b)
Lödöse	155 664	2 662	Årsrapport (2013b)
Nygård	28 357	0	Årsrapport (2013c)
Älvängen	69 922	29 871	Miljörapport (2013e)
Diseröd	115 169	42	Miljörapport (2013a)

The *TF* was calculated using equation [18] and the parameters in the equation are described in Table 21.

$$TF = 1 - \frac{F_{overflow}}{F_{annual,tot}} \quad [18]$$

Table 21: Description of the parameters in equation [18].

Parameter	Symbol	Unit
Treated fraction of the annual flow in a WWTP	*TF*	-
The annual total flow through a WWTP	$F_{annual,tot}$	m^3/year
The total annual overflow at a WWTP	$F_{overflow}$	m^3/year

The calculated *TFs* based on the information in Table 20 and equation [18] for each WWTP are presented in Table 22.

Table 22: The treated fraction (*TF*) in each WWTP.

WWTP	*TF* [-]
Vänersborg, Holmängen	0.99983
Trollhättan, Arvidstorp	0.91961
Hjärtum	1
Lilla Edet, Ellbo	0.9544
Lödöse	0.9829
Nygård	1
Älvängen	0.5728
Diseröd	0.99964

Flow data

The flow data defines the flow in each stretch of the river. The data were mainly obtained as modelled data from SMHI, but also measured data from Vattenfall was collected. Measured data from Vattenfalls four hydropower plants in the Göta Älv river were used when possible, otherwise modelled data were used.

The flow data required by GREAT-ER are the average flow in m^3/s and the low fifth percentile flow in m^3/s. GREAT-ER assumes that the flow is log-normal distributed and characterized by the average flow and the low fifth percentile flow. According to (Wagner et al., 2011), flow data are generally expressed as log-normal distributions.

SMHI offers modelled flow data in certain points, in for example the Göta Älv river, corrected using measured data from monitoring stations through their application called VattenWebb (SMHI, 2014). SMHI has one station in Göta Älv at Vargön at the outflow of Vänern into the river where the flow is measured. The model used by SMHI to model the flow is the hydrological model S-HYPE. In the S-HYPE model, the Göta Älv river is divided into several sub-basins, each ending up at an outlet point where the flow data is modelled. The modelled flow data, corrected with the aid of measured data from SMHI, was generated in the form of average daily flow in m^3/s for each day from 1999 to 2012. The average flow in m^3/s and the low fifth percentile flow in m^3/s were calculated based on this data.

Measured flow data was received from Vattenfall via Mårtensson (2014b) for their four water power plants in the Göta Älv river; Vargön, Hojum, Olidan and Lilla Edet. The water power plants Hojum and Olidan are both situated in Trollhättan and are located close to each other. Therefore, data for the flow through these plants were not given separately but as an average. The flow data for the water power plants Vargön, Hojum and Olidan together and Lilla Edet from Vattenfall was given in the form of average daily flow in m^3/s for the period of 1999-01-01 to 2013-12-31. The average and the low fifth percentile in m^3/s were calculated based on this data.

In GREAT-ER, data on the water velocity, in the form of mean and fifth percentiles in [m/s], and depth, mean and fifth percentile both in [m] can also be specified for each river stretch. However, this information is not compulsory. The velocity and depth for each river stretch were not specified in this study.

Nygård WWTP discharges into the stream Gårdaån and not directly into Göta Älv. The modelled value of the flow that discharges into the Göta Älv was used as an estimate of the flow in Gårdaån. In reality, the flow that discharges into the Göta Älv river consists of flows from several streams, and Gårdaån is just one of them. Because of limited flow data, the flow that discharges into the Göta Älv was used also for Gårdaån. Therefore, the flow in Gårdaån is overestimated. This is important to have in mind when the exposure and effects assessments are evaluated in chapter 4 since it implies that the concentrations of pharmaceuticals in Gårdaån is underestimated.

Implementation of the catchment in GREAT-ER

When all the required information for creating a catchment had been collected and the segmentation of the river into stretches had been conducted, the catchment data was implemented in GREAT-ER by writing eight different text files. These files are the:

- info file,
- digital river network file,
- river network attributes file,
- discharge site data file,
- catchment boundary polygon file,
- background data file,
- lakes file and
- pictures file

All files can be seen in Appendix 7.2. The catchment data had to be written into the text files in certain formats for the GREAT-ER pre-processing programme. These formats are described in each text file respectively.

The final catchment of the Göta Älv river that was developed in GREAT-ER, based on the catchment data described in this section, can be seen in Figure 8. Figure 8 can be compared with the map of the study area in Figure 1.

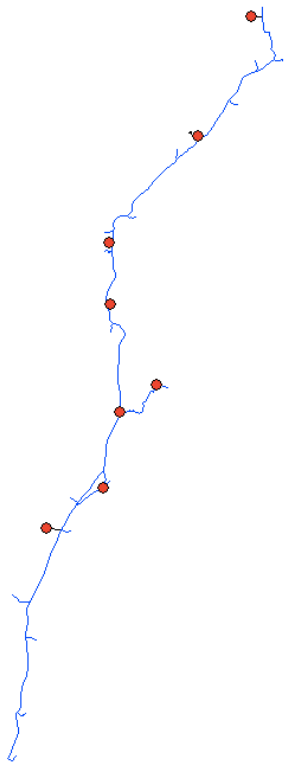


Figure 8: The catchment of the studied part of the river of Göta Älv implemented in GREAT-ER. The red dots in the figure are the WWTPs.

3.3.9 Presentation of results from simulations in GREAT-ER

GREAT-ER offers several ways to present results from simulations. After a simulation, the user encounters a colour-coded map that illustrates PECs in each stretch of the catchment. A $PEC_{catchment}$ value and a RQ can be calculated. The $PEC_{catchment}$ value is weighted with stretch volume, stretch length or by flow increment and can be calculated for all stretches or only for loaded stretches.

RQs can be visualized in a colour-coded map of the catchment and the results can also be seen in a table in the program and the table can be exported as a csv-file that can be imported into Excel. Concentration profiles can also be created for different parts of the catchment.

3.4 Effects assessment

In the exposure assessment, simulations were performed with GREAT-ER for each selected pharmaceutical. In this section, the procedure of gathering information regarding the substance data parameter PNEC is described.

3.4.1 Chronic toxicity data - PNEC

Toxicity data for the selected pharmaceuticals and for the two fish species *Salmo salar* and *Salmo trutta* was searched for in the ecotoxicology database ECOTOX (2014d). The database was created by the U.S. EPA and is a source for finding single chemical toxicity data for aquatic life, terrestrial plants and wildlife (ECOTOX, 2014a). The U.S. EPA also maintains the database.

Some common measures in the evaluation of dose-response relationships are for example the median lethal concentration (LC50) and the median effective concentration (EC50) (Burgman, 2005). A lethal concentration is the concentration at which a certain percentage, 50 % in the case of LC50, of the test organisms has died within a specified time. While an effective concentration is the concentration at which a certain percentage, 50 % in the case of EC50, of the test organisms exhibits a specified response within a specified time. The specified response, or measurement endpoint, is usually acute that means that it is short-term and considered to be severe or lethal (Burgman, 2005).

In the search for toxicity data in ECOTOX, acute toxicity data in the form of effective concentrations for *Salmo salar* and *Salmo trutta* were preferred to derive chronic PNECs from. However, acute toxicity data in the form of effective concentrations were in general not found for the assessment endpoints and the selected pharmaceuticals. For example, such toxicity data were not found at all for the selected pharmaceuticals in the ECOTOX database for *Salmo salar* and only for a few of the pharmaceuticals for *Salmo trutta* (ECOTOX, 2014d). Therefore, due to the difficulties in finding acute toxicity data in the form of effective concentrations, the lowest no observed effect concentration (NOEC) was chosen instead in first case as the toxicological endpoint for a pharmaceutical. When no NOEC could be found, the lowest observed effect concentration (LOEC), more specifically the lowest LOEC that could be found, was chosen. Toxicity data was primarily chosen for *Salmo salar* and *Salmo trutta*. In second hand, toxicity data was selected for species from the same genus, *Salmo*. If such data were not available, toxicity data for fishes from other genus, families and orders were used. The collected toxicity data for all selected pharmaceuticals (Table 3) are presented in Table 23.

Table 23: Toxicity data. The data collected from ECOTOX (2014d) are listed with the aquatic result # and reference # from the database. NOEC and LOEC stands for no observed effect concentration and lowest observed effect concentration respectively. The effect abbreviations: HIS - Histology, PHY - Physiology, ENZ - Enzyme(s), BCM - Biochemistry, GEN - Genetics and MOR - Mortality.

Substance	CAS-number	Toxicity endpoint [unit]	Effect	Species	Toxicity endpoint value	Aquatic result #	Reference #
Diclofenac	15307-86-5	NOEC [µg/l]	HIS	*Salmo trutta*	6.6	2014270	105715
Propranolol	525-66-6	NOEC [mmol/l]	PHY	*Oncorhynchus mykiss*	0.1	2145916	158636
Carbamazepine	298-46-4	NOEC [µg/l]	ENZ	*Oncorhynchus mykiss*	0.89	2044839	155077
Ethinylestradiol	57-63-6	NOEC [µg/l]	BCM	*Salmo salar*	0.005	776084	100690
		NOEC [µg/l]	BCM	*Salmo trutta*	0.0011	2011893	114775
Ibuprofen	15687-27-1	NOEC [µg/l]	ENZ	*Oncorhynchus mykiss*	1 000	2157719	155059
Metoprolol	51384-51-1	NOEC [µg/l]	HIS	*Oncorhynchus mykiss*	5	2051279	153611
Gemfibrozil	25812-30-0	NOEC [µg/l]	GEN	*Danio rerio*	0.38	2051918	157685
Estradiol	50-28-2	NOEC [µg/l]	ENZ	*Salmo salar*	0.008	773382	95928
		NOEC [µg/l]	BCM	*Salmo trutta*	0.015	2011950	114775
Paracetamol (Acetaminophen)	103-90-2	LOEC [µg/l]	GEN	*Salmo salar*	55	2159173	156374
Sertraline	79617-96-2	NOEC [µg/l]	MOR	*Oncorhynchus mykiss*	100	2013160	119228
Verapamil	52-53-9	NOEC [µg/l]	BCM	*Oncorhynchus mykiss*	270	2053586	157815
Estrone	53-16-7	NOEC [µg/l]	BCM	*Salmo trutta*	0.063	2011979	114775

Toxicity data were found for fish from the same family, *Salmoniformes*, as the assessment endpoints for all the selected pharmaceuticals except gemfibrozil. Toxicity data for gemfibrozil was found for *Oncorhynchus mykiss,* which also is from the family of Salmoniformes, but in the unit of amount per bodyweight, not a water concentration that is the unit used to assess the risk in this study. Therefore, toxicity data for *Danio rerio* was used instead.

All toxicity data in Table 23 are given in µg/l except for propranolol, which is given in mmol/l. Therefore, NOEC for proranolol had to be calculated into µg/l, and this was done by multiplying the NOEC, recalculated into mol/l, with the molecular weight of propranolol in µg/mol. The molecular weight of propranolol is approx. 259.3 g/mol (PubChem, 2014). Thus, NOEC for propranolol was calculated to be 25 930 µg/l (Table 27).

The toxicity data in the form of the lowest found NOEC, or LOEC, values for each pharmaceutical were evaluated in order to establish whether the data could be seen as chronic or not (Table 24). The potential of the toxicity data to be seen as chronic was evaluated based on exposure duration and the life stage and/or the age of the test species. The toxicity data was seen as chronic if the exposure duration was over a larger part of the test species life

cycle or if the exposure took place during a specific sensitive period in the test species life. A sensitive period can be when the test species are embryos or juveniles.

Table 24: Evaluation of the toxicity data (Table 23) whether it can be seen as chronic or not based on exposure duration and the life stage and/or age of the test species.

Substance	Reference #	Exposure duration	Life stage and/or age	Comment
Diclofenac	105715	21 days	About 18 months	Not chronic
Propranolol	158636	30 minutes	Embryos, 22 stages	Seen as chronic
Carbamazepine	155077	42 days	10-12 months	Seen as chronic
Ethinylestradiol	100690	3 days	Immature organisms	Seen as chronic
	114775	10-12 days	Sexually immature organism(s)	Seen as chronic
Ibuprofen	155059	96 hours	Fry	Seen as chronic
Metoprolol	153611	28 days	1.5 year	Not chronic
Gemfibrozil	157685	14 days	Not reported	Not chronic
Estradiol	95928	102 days	Not reported	Not chronic
	114775	8 days	Sexually immature organism(s)	Seen as chronic
Paracetamol (Acetaminophen)	156374	5 days	Parr, 12 months	Seen as chronic
Sertraline	119228	96 hours	Juveniles	Seen as chronic
Verapamil	157815	96 hours	Juveniles	Seen as chronic
Estrone	114775	10 days	Sexually immature organism(s)	Seen as chronic

In Table 24, fry indicates newly hatched fishes and parr implies a young salmon or trout at the life stage after being a fry.

The effect in Table 23 is connected to the toxicity endpoint value. For many of the studied pharmaceuticals, toxicity endpoints existed for several types of effects. However, all are not included in Table 23, since only the lowest NOEC, or in one case LOEC, was chosen. Some examples of the effects for which toxicity endpoints usually could be found in ECOTOX (2014d) are biochemistry (BCM), genetic(s) (GEN) and enzyme(s) (ENZ) but also cell(s) (CEL), growth (GRO), hormone(s) (HRM), physiology (PHY) and morphology (MPH) (ECOTOX, 2014b).

When a conclusion had been made regarding if the toxicity data could be seen as chronic or not (Table 24), AFs were used to derive chronic PNECs when it was needed (Table 25). The uncertainty of extrapolating toxicity data from other species to the assessed species *Salmo salar* and *Salmo trutta* were also accounted for by using AFs. The different AFs used to derive chronic PNECs for assessed species for the selected pharmaceuticals are presented in Table 25.

Table 25: AFs used to derive chronic PNECs. The type of AFs and their sizes recommended by Calabrese and Baldwin (1993) and from van Leeuwen and Vermeire (2007) are presented.

Type of AF	Size of AF	Reference
Species with genus	10	Calabrese and Baldwin (1993)
Genera within family	30	Calabrese and Baldwin (1993)
Orders within class	100	Calabrese and Baldwin (1993)
From LOEC to NOEC	10	Calabrese and Baldwin (1993)
From acute NOEC to chronic NOEC	10	van Leeuwen and Vermeire (2007)

Salmo salar and *Salmo trutta* are for example species within genus. In Table 26 are the class, order, family, genus and species listed for the test species for which toxicity data was found (Table 23).

Table 26: Information about the class, order, family, genus and species for the test species of *Salmo salar*, *Salmo trutta*, *Oncorhynchus mykiss* and *Danio rerio*, for which toxicity data was gathered from ECOTOX (2014c).

	Scientific name - Common name			
	Salmo salar - *Atlantic salmon*	*Salmo trutta* - *Brown trout*	*Oncorhynchus mykiss* - *Rainbow trout*	*Danio rerio* - *Zebra danio*
Class	Actinopterygii	Actinopterygii	Actinopterygii	Actinopterygii
Order	Salmoniformes	Salmoniformes	Salmoniformes	Cypriniformes
Family	Salmonidae	Salmonidae	Salmonidae	Cyprinidae
Genus	Salmo	Salmo	Oncorhynchus	Danio
Species	Salar	Trutta	Mykiss	Rerio

The calculated AFs that were used to derive chronic PNECs for *Salmo salar* and *Salmo trutta* for each pharmaceutical are presented in Table 27.

Table 27: AFs used to derive chronic PNECs for *Salmo salar* and *Salmo trutta* for each pharmaceutical.

Substance	Toxicity endpoint [unit]	Comment	Species	Toxicity endpoint value	AF to derive Chronic PNEC, Salmo salar	AF to derive Chronic PNEC, Salmo trutta
Diclofenac	NOEC [µg/l]	Not chronic	*Salmo trutta*	6.6	10 x 10	10
Propranolol	NOEC [µg/l]	Seen as chronic	*Oncorhynchus mykiss*	25 930	30	30
Carbamazepine	NOEC [µg/l]	Seen as chronic	*Oncorhynchus mykiss*	0.89	30	30
Ethinylestradiol	NOEC [µg/l]	Seen as chronic	*Salmo salar*	0.005	-	
	NOEC [µg/l]	Seen as chronic	*Salmo trutta*	0.0011		-
Ibuprofen	NOEC [µg/l]	Seen as chronic	*Oncorhynchus mykiss*	1 000	30	30
Metoprolol	NOEC [µg/l]	Not chronic	*Oncorhynchus mykiss*	5	10 x 30	10 x 30
Gemfibrozil	NOEC [µg/l]	Not chronic	*Zebra danio*	0.38	100 x 10	100 x 10
Estradiol	NOEC [µg/l]	Not chronic	*Salmo salar*	0.008	10	
	NOEC [µg/l]	Seen as chronic	*Salmo trutta*	0.015		-
Paracetamol (Acetaminophen)	LOEC [µg/l]	Seen as chronic	*Salmo salar*	55	10	10 x 10
Sertraline	NOEC [µg/l]	Seen as chronic	*Oncorhynchus mykiss*	100	30	30
Verapamil	NOEC [µg/l]	Seen as chronic	*Oncorhynchus mykiss*	270	30	30
Estrone	NOEC [µg/l]	Seen as chronic	*Salmo trutta*	0.063	10	-

The chronic PNEC was calculated by dividing the toxicity endpoint value with the calculated AF (Table 27). The resulting chronic PNECs for *Salmo salar* and *Salmo trutta* are presented in µg/l in Table 31, see section 4.2.

3.5 Risk characterization

In order to be able to draw any conclusions regarding potential risks with the exposure of pharmaceuticals to fish in the river, possible effect levels resulting from the exposure must be assessed. Therefore, the results from the hazard identification, exposure assessment and effect assessment must be combined in order to characterize the risk. This section describes how this combination of information was performed.

3.5.1 Toxicity of individual pharmaceuticals

The toxicity of the individual pharmaceuticals to the endpoints *Salmo salar* and *Salmo trutta* was assessed by calculating risk quotients in GREAT-ER, see equation [19].

$$RQ_{i,j} = \frac{PEC_i}{PNEC_{i,j}} \quad [19]$$

In equation [19], $RQ_{i,j}$ is the risk quotient for chemical i and assessment endpoint j. If $RQ_{i,j}$ exceeds one it was assessed to be a risk for adverse effects for the assessment endpoint.

The options to analyse the simulation results in GREAT-ER provided the opportunity to create colour-coded maps for the geographical distribution of RQs in the catchment. These maps are presented in section 4.1.

The results from the risk characterization of individual pharmaceuticals can be seen in section 4.3.1.

3.5.2 Mixture toxicity

Mixture effects are generally neglected in assessments of risk, which in general only is assessed for the individual chemicals. However, this may result in underestimations of the risk according to Backhaus and Faust (2012). In general, in nature, many substances are present at the same time and thus endpoints are usually exposed to a mixture of substances. In order to assess mixture toxicity effects, the concept of concentration addition (CA) was used as a first conservative tier based on Backhaus and Faust (2012) and Vaj et al. (2011). Another concept that can be used to calculate mixture effects for mixtures of substances with different mode of action is independent action (IA). However, IA was not used in this study. In both CA and IA it is assumed that the substances in the mixture affect the same endpoint and that there are no interaction between the substances so that their uptake, distribution or metabolization is not influenced by each other. This is of course a simplification.

CA is a well-established model used to estimate mixture toxicity for similar acting substances, which are substances that have the same mode of action. In Table 3 showing the selected stressors, it can be seen that the studied pharmaceuticals are from several therapeutic groups. They can therefore be expected to have quite different modes of action, implying that the utilization of the concept of CA can be questioned. However, mixture toxicities that are higher than the ones predicted by CA are uncommon. Therefore, according to Backhaus and Faust (2012) the concept of CA can be used as a conservative first tier, independent of the mode of action of the substances.

In the CA concept, the estimated mixture toxicity is calculated by summing up the RQs for the assessment endpoint *j* and for all the substances *i* in a mixture of *n* components according to Backhaus and Faust (2012) and equation [20].

$$RQ_{mix,CA,j} = \sum_{i=1}^{n} RQ_{i,j} = \sum_{i=1}^{n} \frac{PEC_i}{PNEC_{i,j}} \quad [20]$$

A fundamental assumption of CA is that the individual toxicity data is affecting the same organism (Backhaus and Faust, 2012). If PNECs for different organisms are used, this certainly violates this assumption. The PNECs can also be derived by using different AFs which according to Backhaus and Faust (2012) can make the resulting sum difficult to interpret. Backhaus and Faust (2012) assume that a base set of data including acute toxicity data, more precise EC50 values, is available and that the same AF can be used to derive PNECs from the acute toxicity data. However, in this study acute toxicity data for the species of *Salmo salar* and *Salmo trutta* was rarely found, see section 3.4.1. The NOECs, and in one case LOEC, that were found were sometimes from toxicity tests from other species than *Salmo salar* and *Salmo trutta*. However, this was accounted for by using AFs, but different AFs had to be used for different pharmaceuticals depending on the toxicity data that had been found. Despite this and the fact that acute toxicity data were not used, equation [20] was still utilized and the estimated chronic mixture toxicity was calculated for all the pharmaceuticals and for *Salmo salar* and *Salmo trutta* respectively.

$RQ_{mix,CA,j}$ was based on the RQs calculated by GREAT-ER for each stretch and pharmaceutical. These RQs for each stretch and pharmaceutical made it possible to calculated $RQ_{mix,CA,j}$ for each stretch. The results from the risk characterization of mixtures of the studied pharmaceuticals are presented in section 4.3.2.

3.6 Habitat comparison

A habitat comparison was performed in order to evaluate if there are any fish habitats in the parts of the Göta Älv river where alarming concentrations of pharmaceuticals had been modelled. The habitat comparison was done by comparing the geographical distribution of PECs and RQs with the geographical distribution of known habitats of *Salmo salar* and *Salmo trutta* (Figure 9). The PECs and RQs were obtained from GREAT-ER based on the exposure assessment, effect assessment and risk characterization steps.

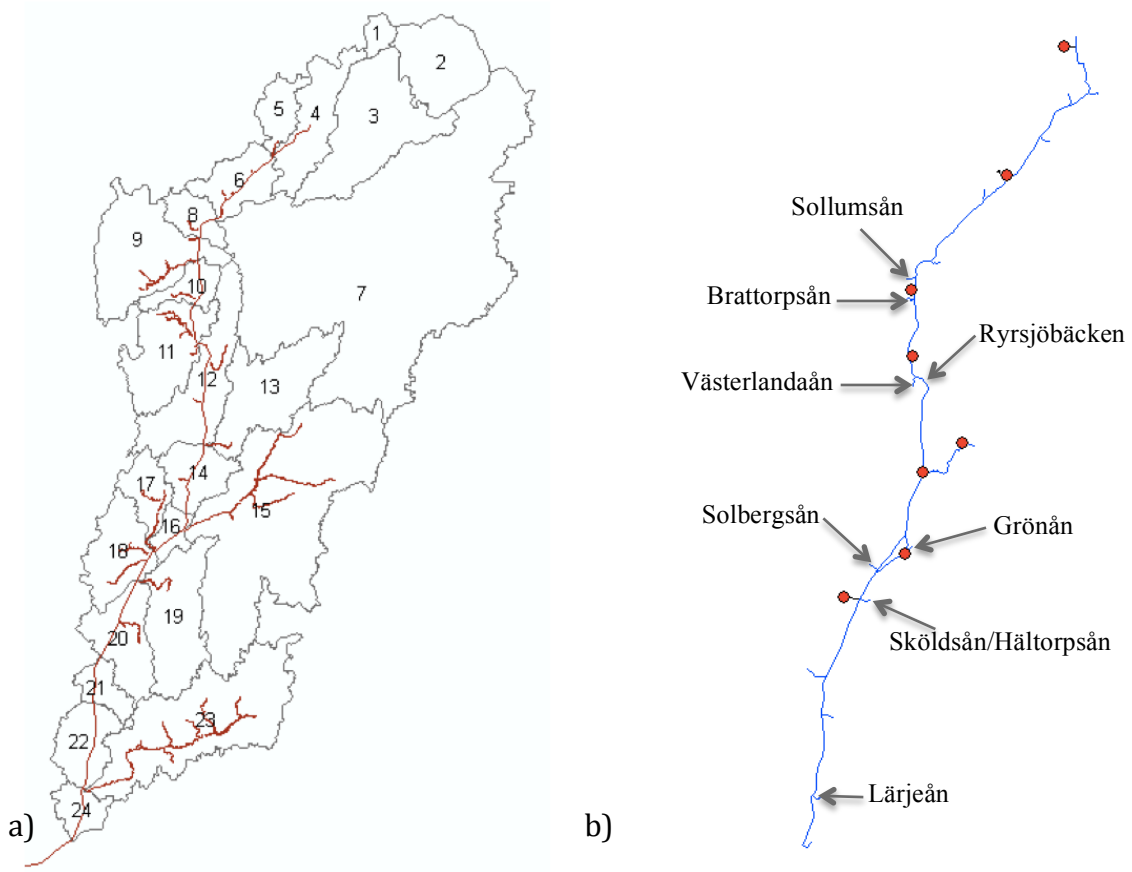


Figure 9: a) Known habitats of *Salmo salar* and *Salmo trutta* obtained from Westerdahl (2009) with permission. b) The location in the catchment of the tributaries identified as being important spawning grounds for *Salmo salar* and *Salmo trutta*.

The map in Figure 9 a) is divided into subareas, numbered in the order that they drain into the river from Vänersborg to Göteborg. According to Westerdahl (2009), some of the tributaries are more important habitats than others for *Salmo salar* and *Salmo trutta* since these are used as spawning grounds. The tributaries that are important spawning grounds for *Salmo salar* and *Salmo trutta* are presented in Figure 9 b) and they are also listed with their adherent subarea in Table 28.

Table 28: Tributaries to the Göta Älv river, with their adherent subarea, that has been identified as important spawning grounds for Salmo salar and Salmo trutta (Westerdahl, 2009).

Tributary	Subarea
Sollumsån	9
Brattorpsån	9
Västerlandaån	11
Ryrsjöbäcken	12
Grönån	15
Solbergsån	17
Sköldsån/Hältorpsån	19
Lärjeån	23

4 Result and discussion

In this chapter, the results from the simulations with GREAT-ER are presented and discussed. The exposure, that is PECs, are presented and risk ratios are given both for individual and mixture toxicity effects. The risk is characterized by comparing the simulation results with the location of known fish habitats in Göta Älv river. Finally, the results are validated through comparison with MECs in Swedish waters. The results are also compared with the results from a simple dilution model created by Westerdahl (2009).

4.1 Exposure assessment

The results from the exposure assessment conducted with the aid of the GREAT-ER model are presented in this section with colour-coded maps of *PEC*s for each studied pharmaceutical in the Göta Älv river. $PEC_{catchment}$ and PEC_{max} values and concentration profiles are also provided for each pharmaceutical.

The $PEC_{catchment}$ value is the average *PEC* for all the stretches in the catchment weighted with stretch volume. The stretch volume is estimated based on data regarding flow, flow velocity and stretch length based on the assumption of a rectangular cross section area (Wagner and Koorman, 2011). Only polluted stretches are considered in the $PEC_{catchment}$ value that is presented in this study. The PEC_{max} value is the maximum *PEC* for the catchment. The values for $PEC_{catchment}$ and PEC_{max} are presented for each pharmaceutical in Table 29. The approximate location of the stretch with the maximum *PEC* in the catchment is marked in the exposure figures for each pharmaceutical that are presented in this section.

Table 29:Modelled $PEC_{catchment}$ and PEC_{max} in the Göta Älv river for the studied pharmaceuticals. $PEC_{catchment}$ is weighted with volume and only considering loaded stretches. Loaded stretches imply stretches that include pharmaceutical residues, for example tributaries to the Göta Älv river are not loaded stretches.

Substance	$PEC_{catchment}$ [pg/l]	PEC_{max} [pg/l]
Diclofenac	180	3 220
Propranolol	53	1 020
Carbamazepine	760	13 000
Ethinylestradiol	1	17
Ibuprofen	480	7 090
Metoprolol	940	16 000
Gemfibrozil	200	3 780
Estradiol	0.90	14
Paracetamol (Acetaminophen)	930	5 780
Sertraline	15	260
Verapamil	26	470
Estrone	8.5	150

Concentration profiles were created for each pharmaceutical for the main part of the Göta Älv river, marked with red in Figure 10. Tributaries and Nordre Älv are not included in the created concentration profiles. The location of the four larger WWTPs; Vänersborg, Trollhättan, Lilla Edet and Älvängen WWTP are marked in the concentration profiles together with the location of the ramification of the river at Kungälv into Nordre Älv and Göta Älv. These locations are marked, since it could be seen in the concentration profiles that these WWTPs and the ramification were clearly affecting the shape of the concentration profile.

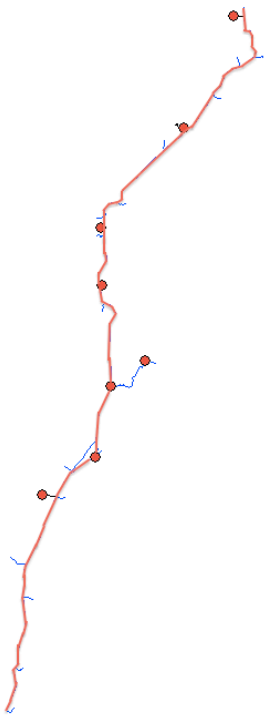


Figure 10: The main stretch, marked with red, of the Göta Älv river for which concentration profiles were created.

Diclofenac

In Figure 11, the exposure of diclofenac in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

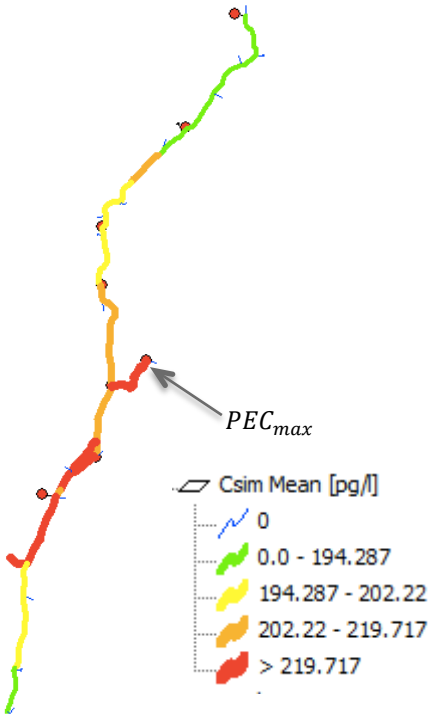


Figure 11: Exposure of diclofenac in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for diclofenac based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 12).

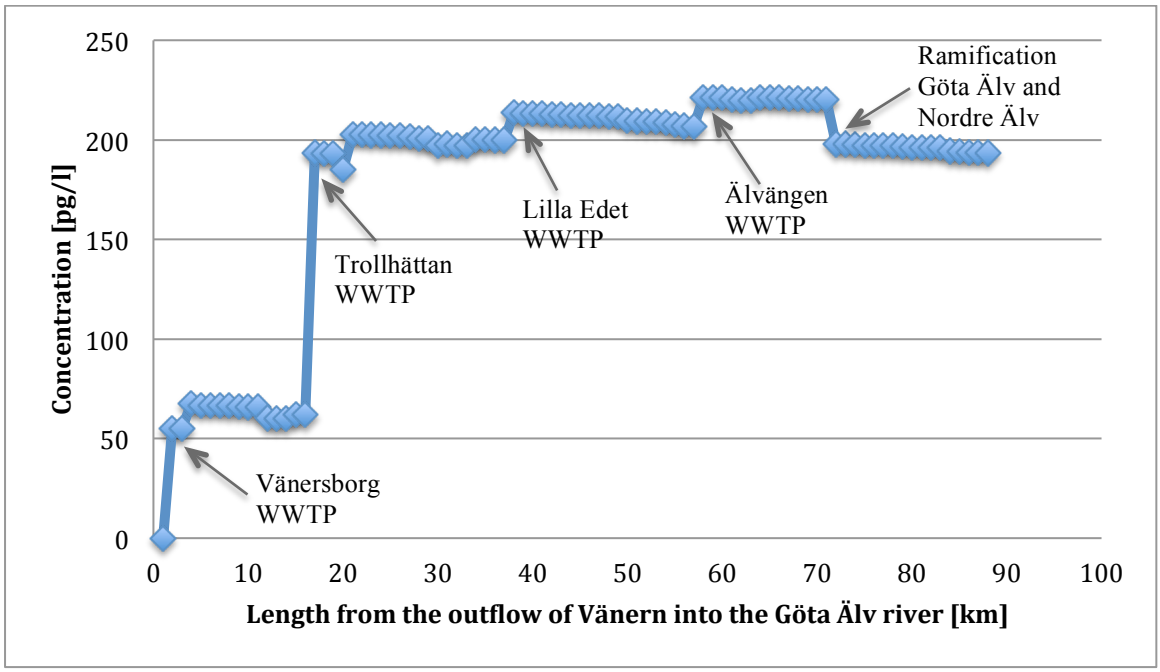


Figure 12: Concentration profile for diclofenac in the Göta Älv river based on data from GREAT-ER.

Propranolol

In Figure 13, the exposure of propranolol in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

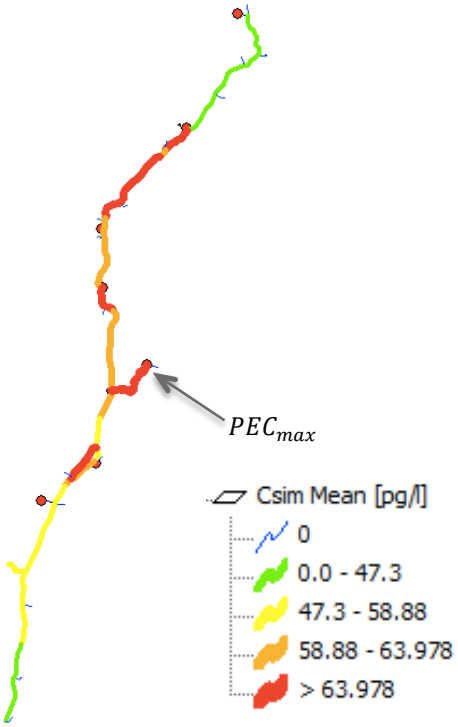


Figure 13: Exposure of propranolol in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for propranolol based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 14).

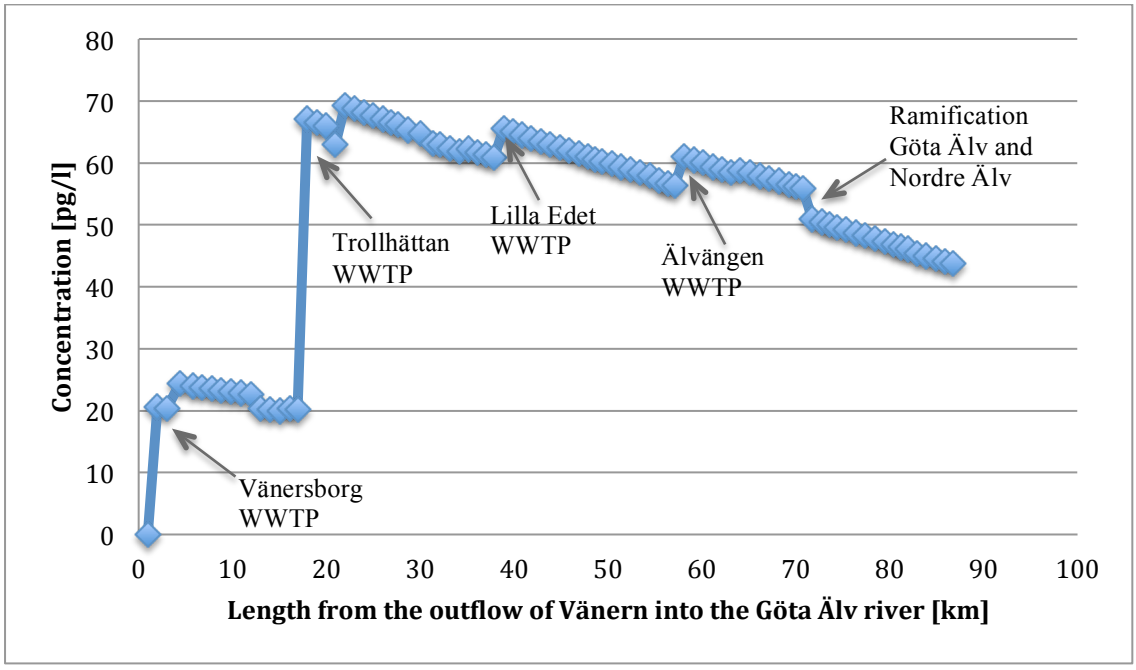


Figure 14: Concentration profile for propranolol in the Göta Älv river based on data from GREAT-ER.

Carbamazepine

In Figure 15, the exposure of carbamazepine in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

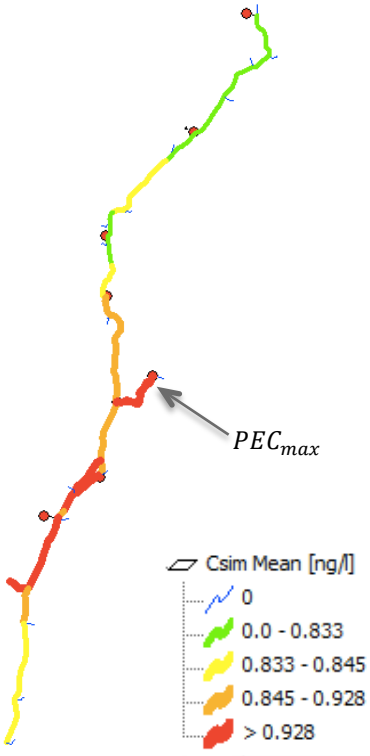


Figure 15: Exposure of carbamazepine in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for carbamazepine based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 16).

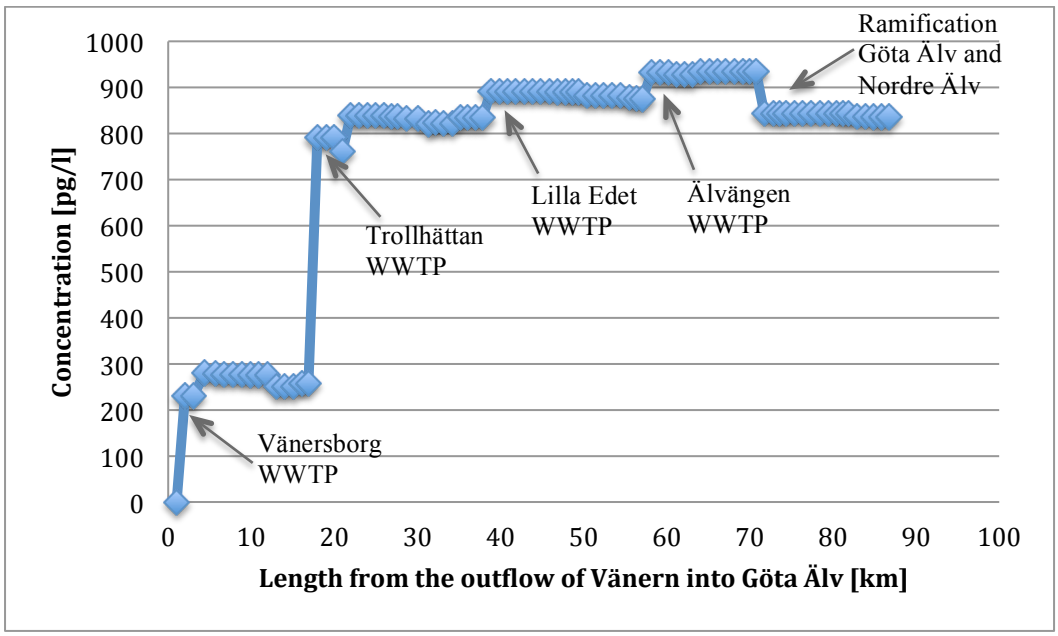


Figure 16: Concentration profile for carbamazepine in the Göta Älv river based on data from GREAT-ER.

Ethinylestradiol

In Figure 17, the exposure of ethinylestradiol in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

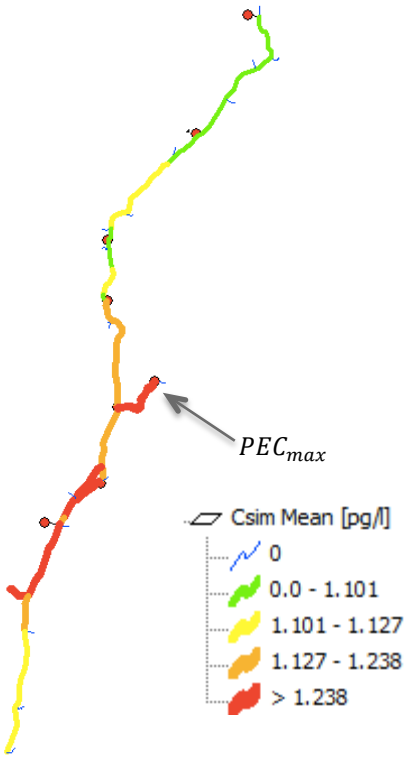


Figure 17: Exposure of ethinylestradiol in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for ethinylestradiol based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 18).

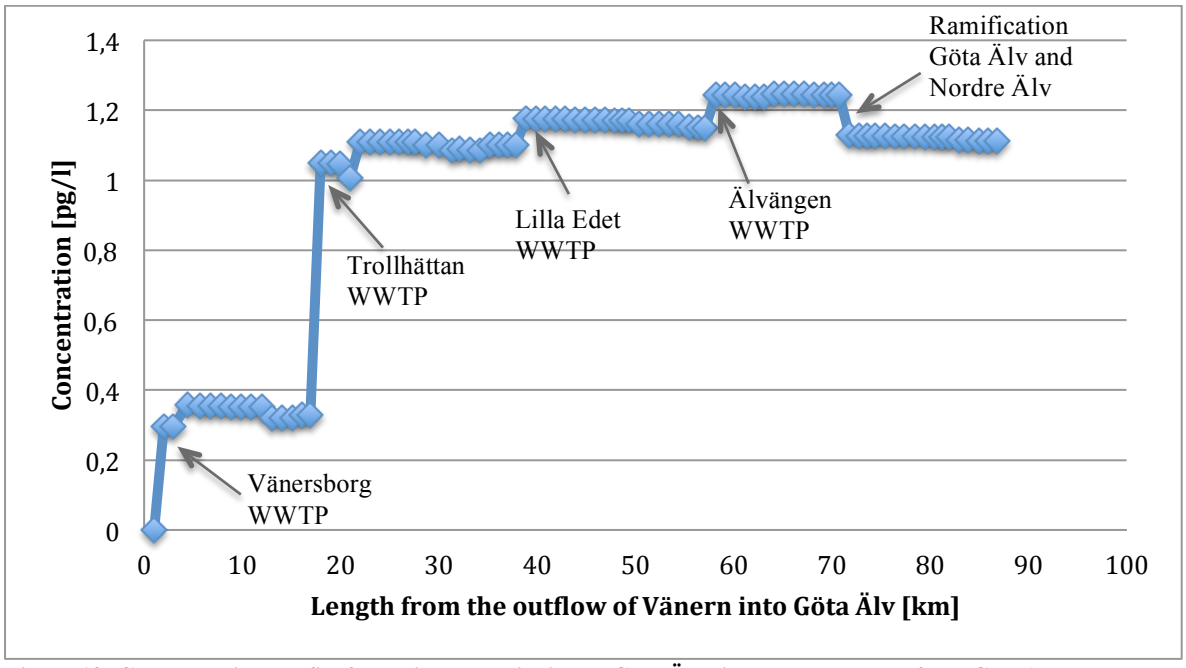


Figure 18: Concentration profile for ethinylestradiol in the Göta Älv river based on data from GREAT-ER.

Ibuprofen

In Figure 19, the exposure of ibuprofen in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

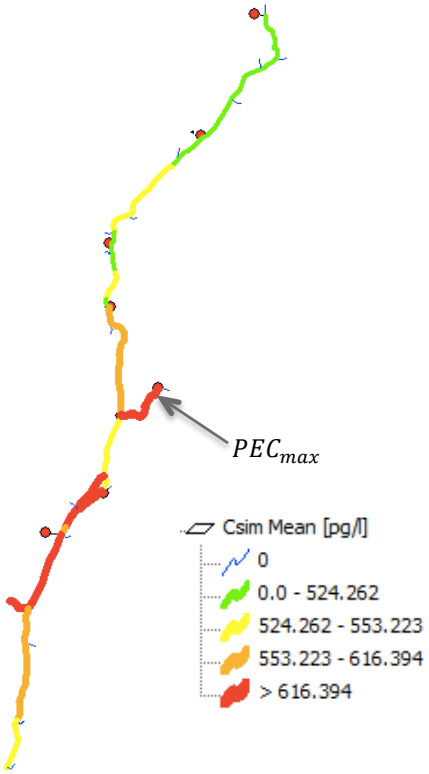


Figure 19: Exposure of ibuprofen in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for ibuprofen based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 20).

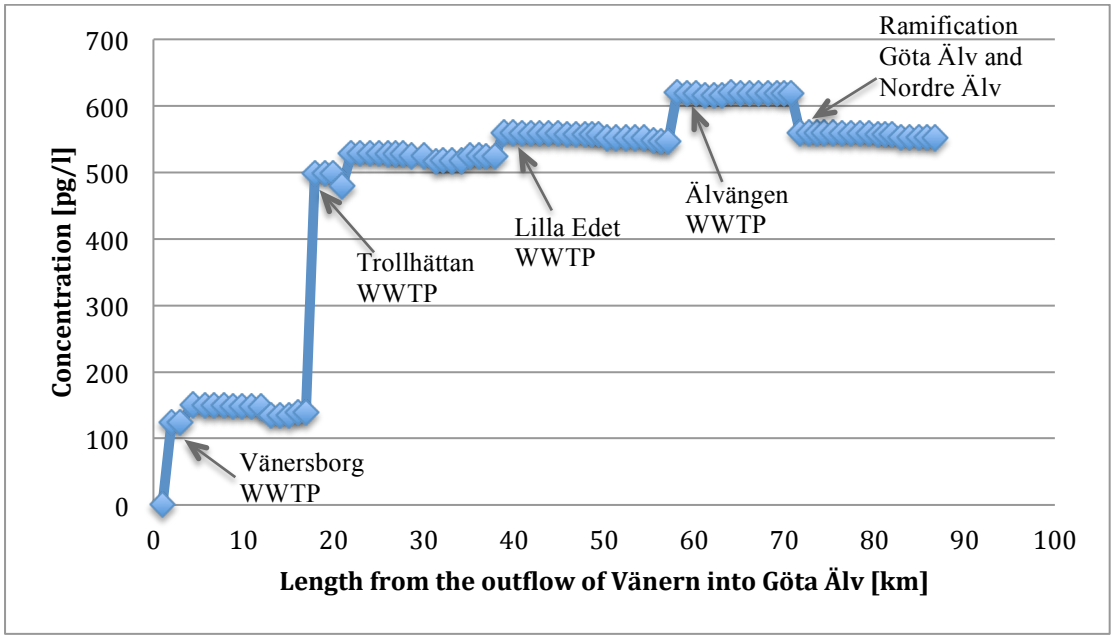


Figure 20: Concentration profile for ibuprofen in the Göta Älv river based on data from GREAT-ER.

Metoprolol

In Figure 21, the exposure of metoprolol in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

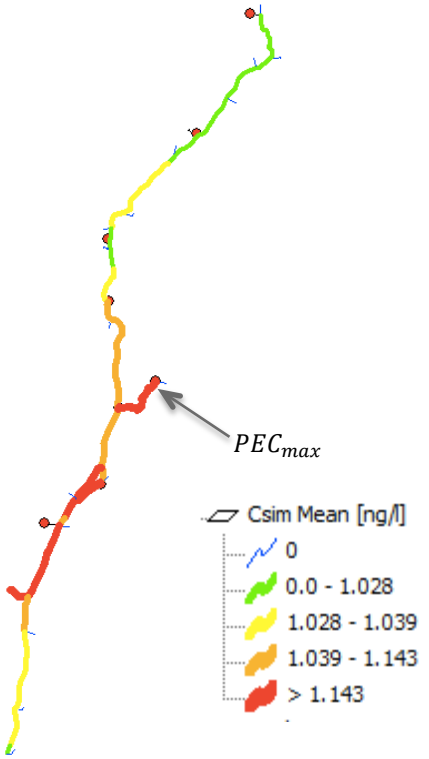


Figure 21: Exposure of metoprolol in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for metoprolol based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 22).

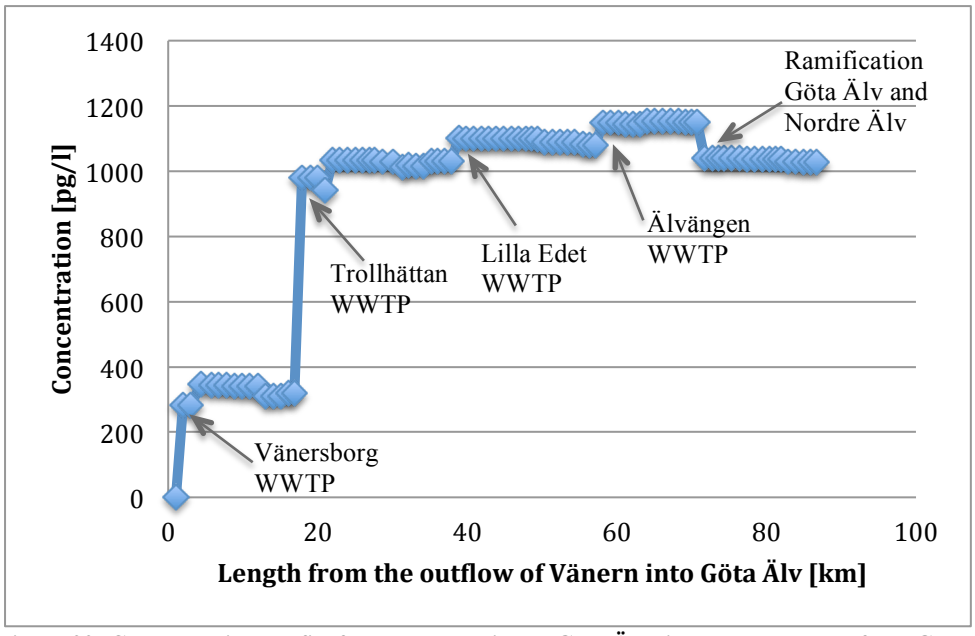


Figure 22: Concentration profile for metoprolol in the Göta Älv river based on data from GREAT-ER.

Gemfibrozil

In Figure 23, the exposure of gemfibrozil in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

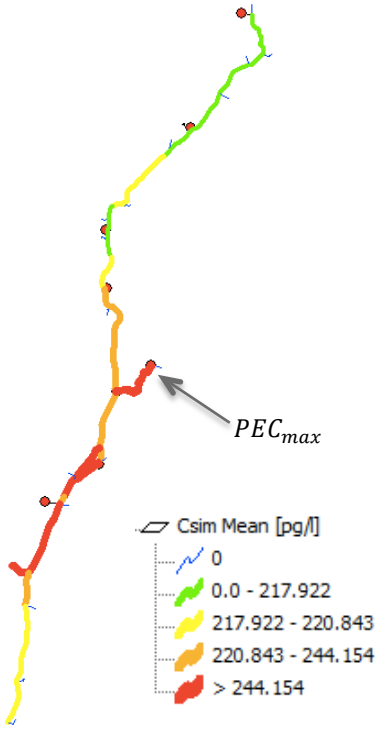


Figure 23: Exposure of gemfibrozil in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for gemfibrozil based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 24).

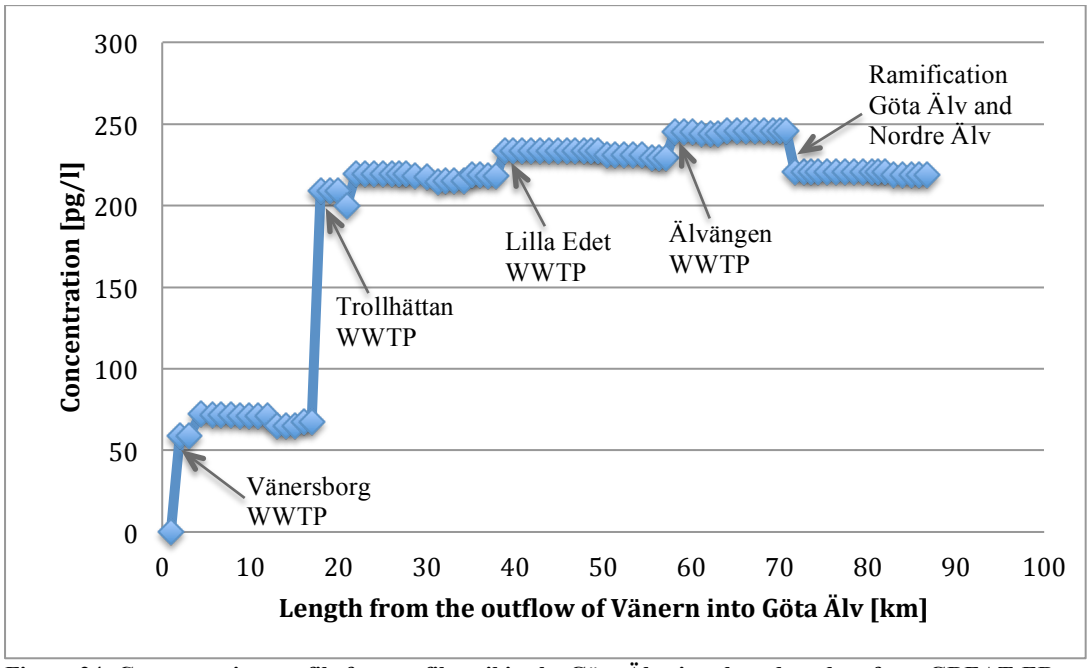


Figure 24: Concentration profile for gemfibrozil in the Göta Älv river based on data from GREAT-ER.

Estradiol

In Figure 25, the exposure of estradiol in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

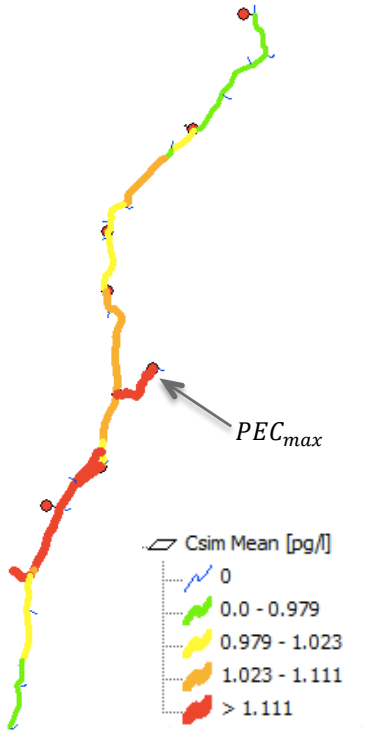


Figure 25: Exposure of estradiol in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for estradiol based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 26).

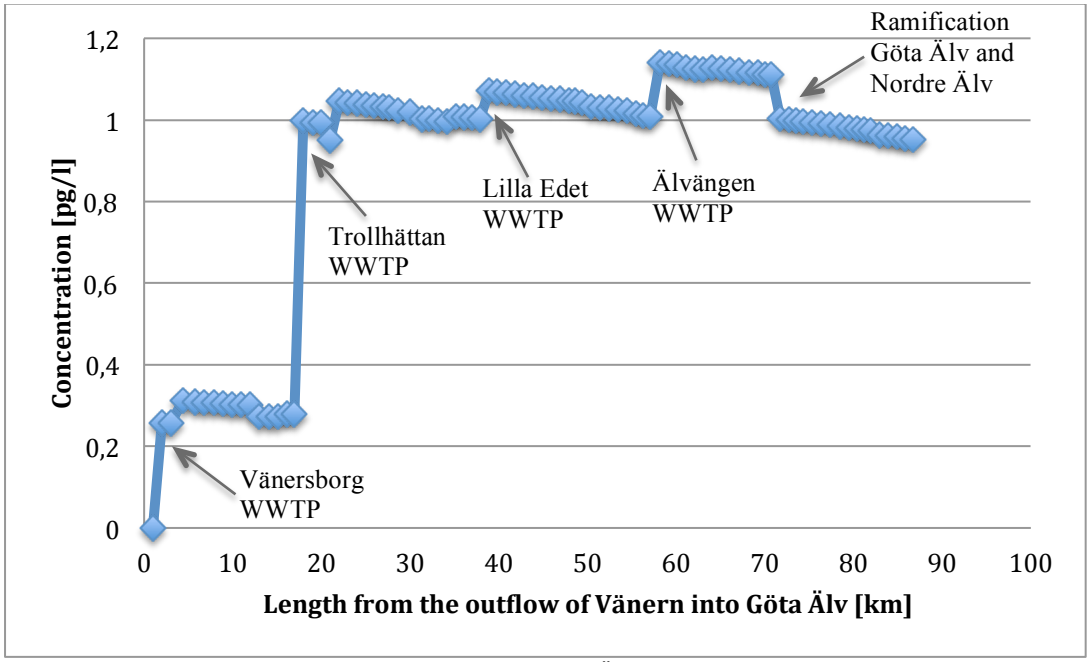


Figure 26: Concentration profile for estradiol in the Göta Älv river based on data from GREAT-ER.

Paracetamol (Acetaminophen)

In Figure 27, the exposure of paracetamol in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

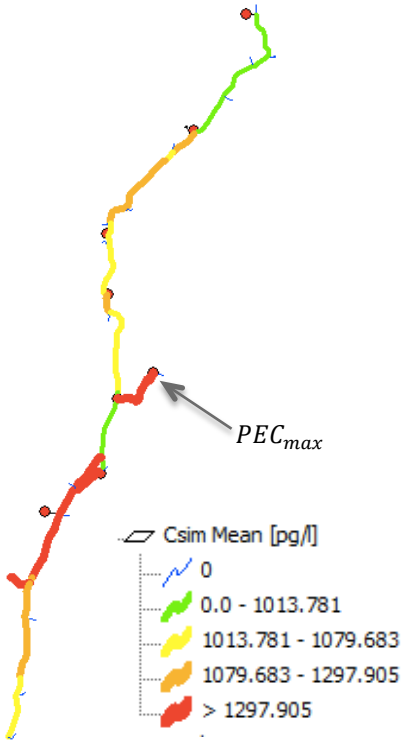


Figure 27: Exposure of paracetamol in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for paracetamol based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 28).

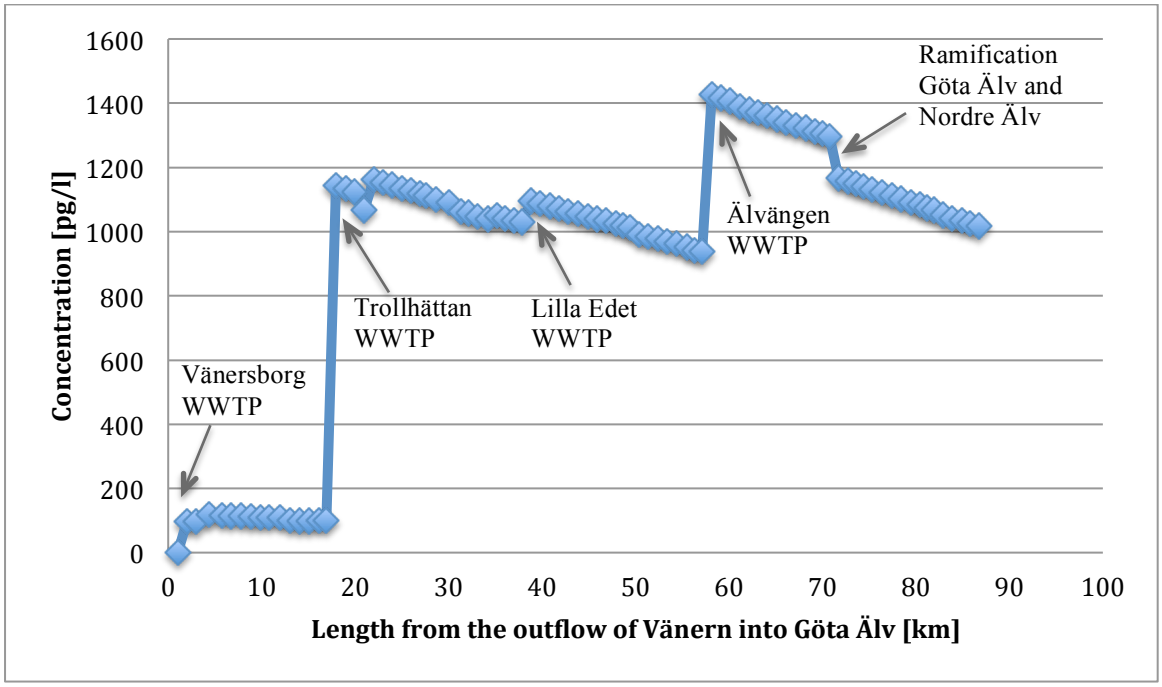


Figure 28: Concentration profile for paracetamol in the Göta Älv river based on data from GREAT-ER.

Sertraline

In Figure 29, the exposure of sertraline in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

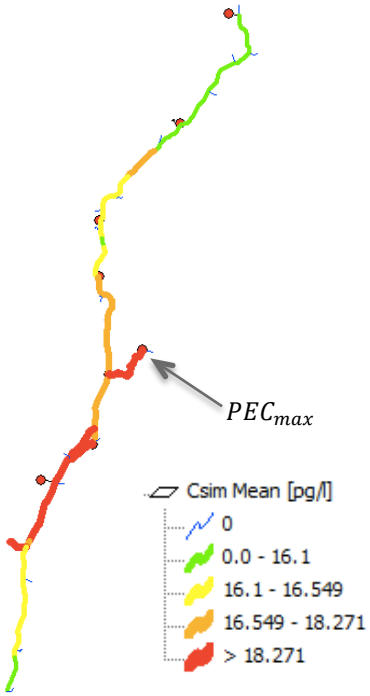


Figure 29: Exposure of sertraline in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for sertraline based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 30).

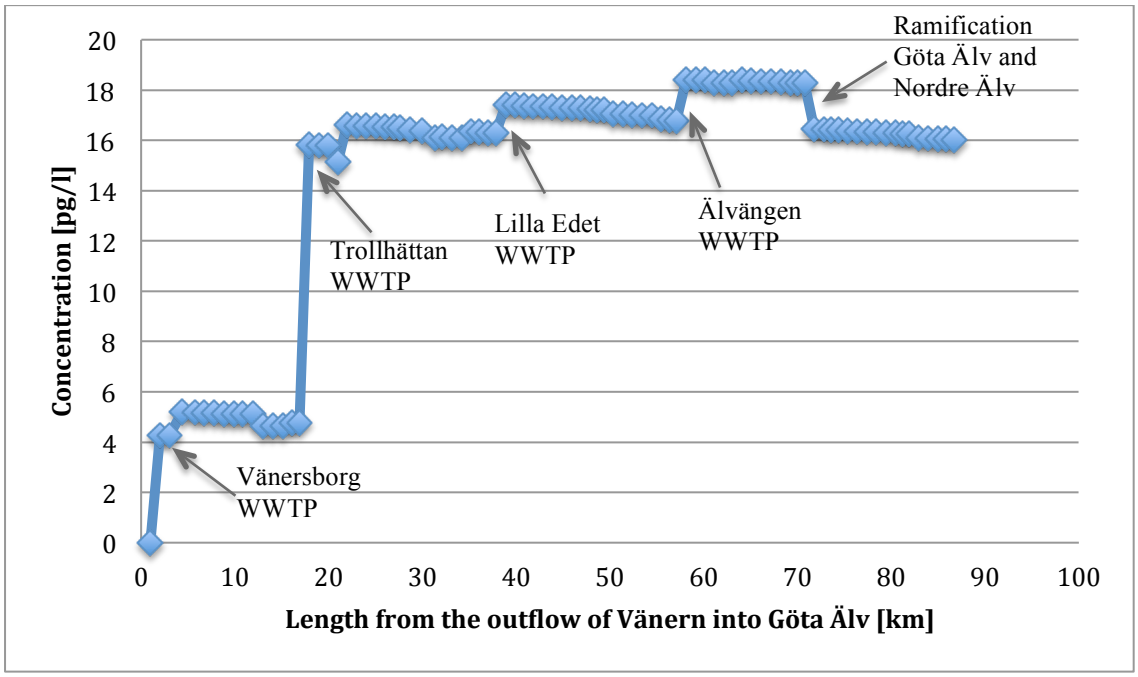


Figure 30: Concentration profile for sertraline in the Göta Älv river based on data from GREAT-ER.

Verapamil

In Figure 31, the exposure of verapamil in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

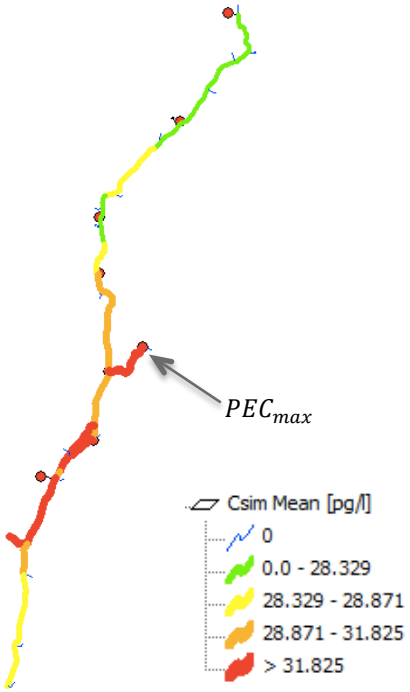


Figure 31: Exposure of verapamil in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for verapamil based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 32).

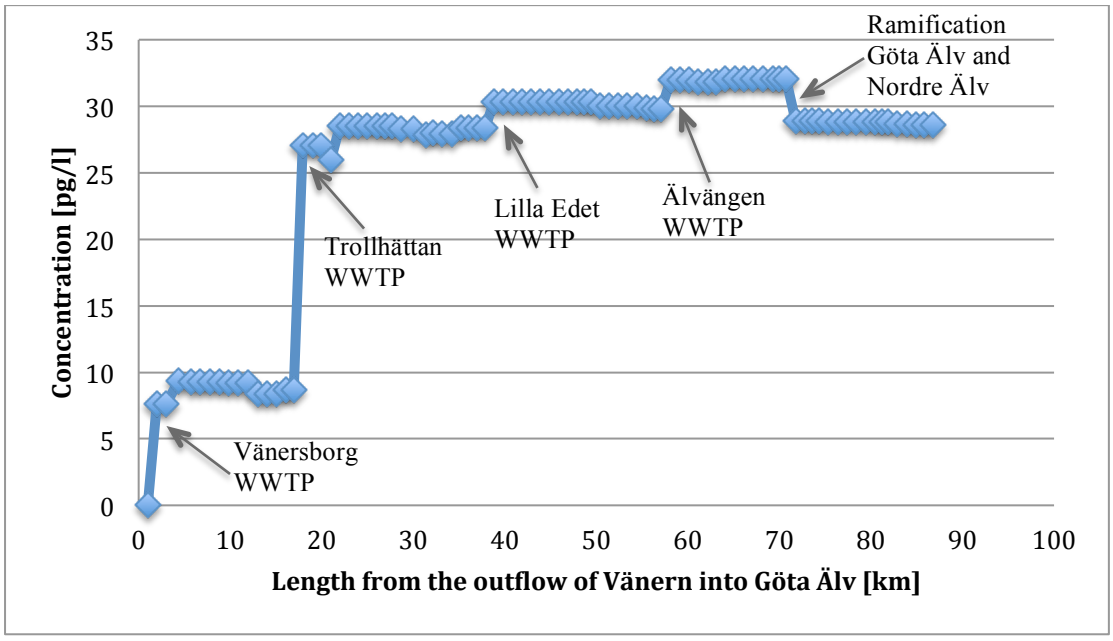


Figure 32: Concentration profile for verapamil in the Göta Älv river based on data from GREAT-ER.

Estrone

In Figure 33, the exposure of estrone in the Göta Älv river is presented together with the approximate location for the stretch with the maximum *PEC*.

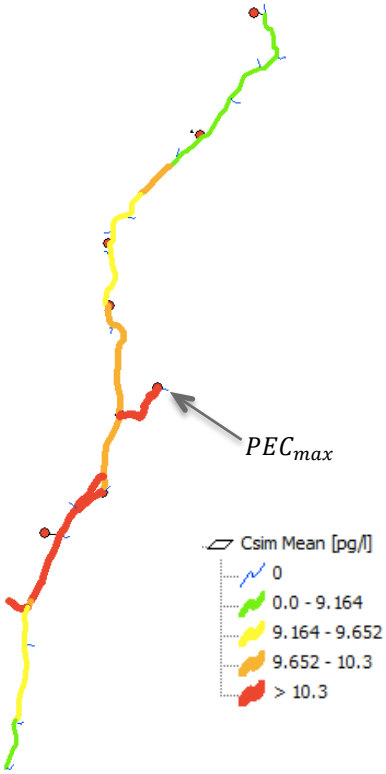


Figure 33: Exposure of estrone in the Göta Älv river simulated with GREAT-ER and the approximate location of PEC_{max}.

A concentration profile was created for estrone based on the simulated average concentrations for each stretch, called $C_{sim,internal}$ in GREAT-ER (Figure 34).

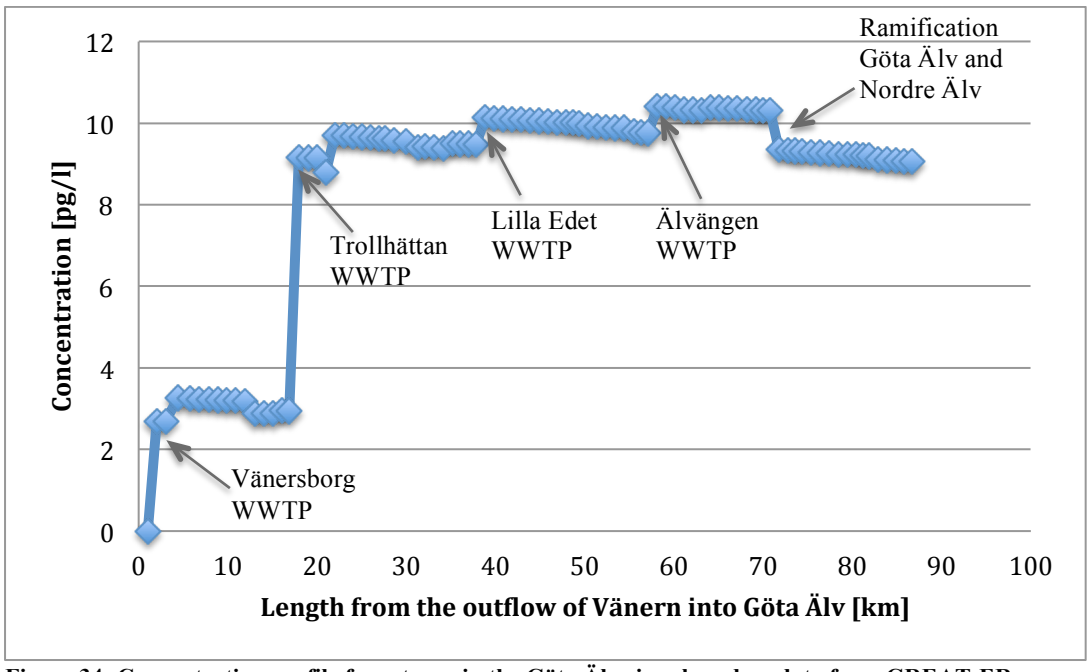


Figure 34: Concentration profile for estrone in the Göta Älv river based on data from GREAT-ER.

Comments on the geographical distribution of PECs

The PECs of pharmaceuticals generally increases downstream the Göta Älv river. This is because more pharmaceuticals are added from the effluents of WWTPs, and the degradation is slow. The geographical distributions of PECs are similar, with the high PECs found in connection to the WWTPs lying most downstream in the river; Älvängen WWTP and Diseröd WWTP. The maximum PECs are found in the tributary Gårdaån to which the Nygård WWTP discharges. Important to mention, is the fact that the flow in Gårdaån is overestimated in this study because of limited flow data and thus the concentrations are underestimated in Gårdaån, see section 3.3.8. An exception to the general geographical distributions of PECs of the studied pharmaceuticals is propranolol (Figure 13). For propranolol, the high PECs were not only found in connection to Nygård WWTP and in the left part of the bifurcation close to Älvängen WWTP (Figure 1 and Figure 13) as for the other pharmaceuticals, but also after Trollhättan and Lilla Edet WWTP.

The reason for this might be a combination of the large emissions of propranolol upstream the Göta Älv river and the large value for the in-stream removal rate (Table 15) for propranolol compared with the other pharmaceuticals, see section 3.2.2. The large upstream emissions of propranolol can be derived from the fact that Trollhättan and Lilla Edet are relatively large WWTPs with large effluents in combination with the negative removal efficiency of propranolol (Table 6). In Table 6, it can be seen that estrone also has a large negative value for R_{WWTP}. However, estrone has a much smaller value for k than propranolol (Table 15). This implies that the concentration of estrone will increase downstream the Göta Älv river to a larger extent than propranolol and thus the larger PEC values for estrone will be found more downstream. This was also the case in this study (Figure 33).

Comments on the concentration profiles

The concentration profiles are generally similar for all pharmaceuticals except for propranolol, estradiol and paracetamol. Generally, PECs increases along the Göta Älv river as more pharmaceuticals reach the river from the WWTPs, and the degradation is very slow. The increase is especially high after Vänersborg, Trollhättan, Lilla Edet and Älvängen WWTP, which have much more people connected than the other WWTPs (Table 17). There is a decrease in the PEC in all concentration profiles at the ramification of Nordre Älv river and Göta Älv river. However, the slopes of the concentration profiles vary. This is due to differences in degradation rates of the pharmaceuticals (k). The PECs for propranolol, estradiol and paracetamol are declining faster than in the concentration profiles for the other pharmaceuticals. In Table 15 in section 3.2.2, it can be seen that the degradation rates (k) for propranolol, estradiol and paracetamol are larger compared with k for the other pharmaceuticals.

4.1.1 Comparison between obtaining *M* with backward calculation and forward calculation

Note that for most pharmaceuticals in Table 30, there is a reasonable, order-of-magnitude, agreement between the two methods for calculating M. However, if M obtained with backward calculation and forward calculation (Table 30) are compared, it can be seen that the values for M obtained with backward calculation generally are higher. One could perhaps think that the values for M obtained with backward calculation should have been lower than the values for M obtained with forward calculation. This is because people most likely do not eat all the pharmaceuticals they buy. This is not considered in the forward calculation. At the same time there did generally exist many more ATC codes for the pharmaceuticals than the ones that sale statistics were given for in this study. However, all ATC codes were not included since there was no assigned DDDs for these ATC codes, implying that even if there

existed sale statistics these could not be converted into the right unit of kg/capita and year, see Figure 7.

Table 30: Average M obtained with backward and forward calculation.

Substance	Average $M_{Backward\ calc}$ [kg/(capita*year)]	Average $M_{Forward,calc}$ [kg/(capita*year)]
Diclofenac	3.9E-05	6.8E-05
Propranolol	1.3E-05*	4.9E-06*
Carbamazepine	1.4E-04*	1.3E-05*
Ethinylestradiol	3.1E-07	No data
Ibuprofen	3.2E-04	1.4E-3
Metoprolol	1.7E-04*	1.6E-4*
Gemfibrozil	4.4E-05	1.2E-05
Estradiol	5.5E-07	1.0E-07
Paracetamol (Acetaminophen)	2.6E-03	1.8E-3
Sertraline	5.8E-06	8.2E-07
Verapamil	6.1E-06	3.7E-06
Estrone	1.6E-06*	No data

* Corrected due to the requirement in GREAT-ER of values for R_{WWTP} between zero and one, see section 3.3.4 to 3.3.6.

4.2 Effect assessment

The resulting chronic PNECs from the effect assessment in section 3.4.1 are presented in Table 31.

Table 31: Calculated chronic PNECs for *Salmo salar* and *Salmo trutta* based on toxicity data from ECOTOX (2014d) with AFs used from Calabrese and Baldwin (1993) and van Leeuwen and Vermeire (2007).

Substance	CAS-number	Chronic PNEC [µg/l] - *Salmo salar*	Chronic PNEC [µg/l] - *Salmo trutta*
Diclofenac	15307-86-5	0.0663	0.663
Propranolol	525-66-6	864	864
Carbamazepine	298-46-4	0.0297	0.0297
Ethinylestradiol	57-63-6	0.005	0.0011
Ibuprofen	15687-27-1	33	33
Metoprolol	51384-51-1	0.0167	0.0167
Gemfibrozil	25812-30-0	0.00038	0.00038
Estradiol	50-28-2	0.0008	0.0153
Paracetamol (Acetaminophen)	103-90-2	5.48	0.548
Sertraline	79617-96-2	3.33	3.33
Verapamil	52-53-9	9	9
Estrone	53-16-7	0.0063	0.063

4.3 Risk characterization

The potential risk arising from the exposure of pharmaceuticals to *Salmo salar* and *Salmo trutta* in the Göta Älv river were evaluated in the risk characterization step. The results are presented for individual effects and mixture effects separately.

4.3.1 Individual effects

RQs for the individual pharmaceuticals were calculated for *Salmo salar* and *Salmo trutta* for each stretch and pharmaceutical from the simulation results in GREAT-ER. This resulted in colour-coded maps for RQ for each pharmaceutical, which are presented in Figure 35 and Figure 36 while the value for RQ_{max} for each pharmaceutical can be seen in Table 32.

Table 32: RQ_{max} for the studied pharmaceuticals and for *Salmo salar* and *Salmo trutta* respectively.

	RQ_{max}	
Substance	***Salmo salar***	***Salmo trutta***
Diclofenac	0.049	0.0049
Propranolol	1.2E-6	1.2E-6
Carbamazepine	0.45	0.45
Ethinylestradiol	0.003	0.016
Ibuprofen	0.0002	0.0002
Metoprolol	0.97	0.97
Gemfibrozil	9.96	9.96
Estradiol	0.018	0.0009
Paracetamol (Acetaminophen)	0.001	0.011
Sertraline	7.7E-5	7.7E-5
Verapamil	5.2E-5	5.2E-5
Estrone	0.02	0.002

The RQs for the pharmaceuticals; diclofenac, propranolol, ethinylestradiol, ibuprofen, estradiol, paracetamol, sertraline, verapamil and estrone were less than one in the entire catchment (Figure 35 a)). This indicates that there is no risk for adverse effects on *Salmo salar* and *Salmo trutta* for these pharmaceuticals in the Göta Älv river when the pharmaceuticals are considered individually. The RQs for carbamazepine and metoprolol never exceeded one in the catchment but were close in some cases, seen in Figure 35 b) and Figure 36 a). Gemfibrozil was identified as the only pharmaceutical with RQs larger than one for some parts of the catchment, presented in Figure 36 b). Therefore, considering individual effects from gemfibrozil to *Salmo salar* and *Salmo trutta* there might be a risk for adverse effects in some parts of the river for the assessment endpoints.

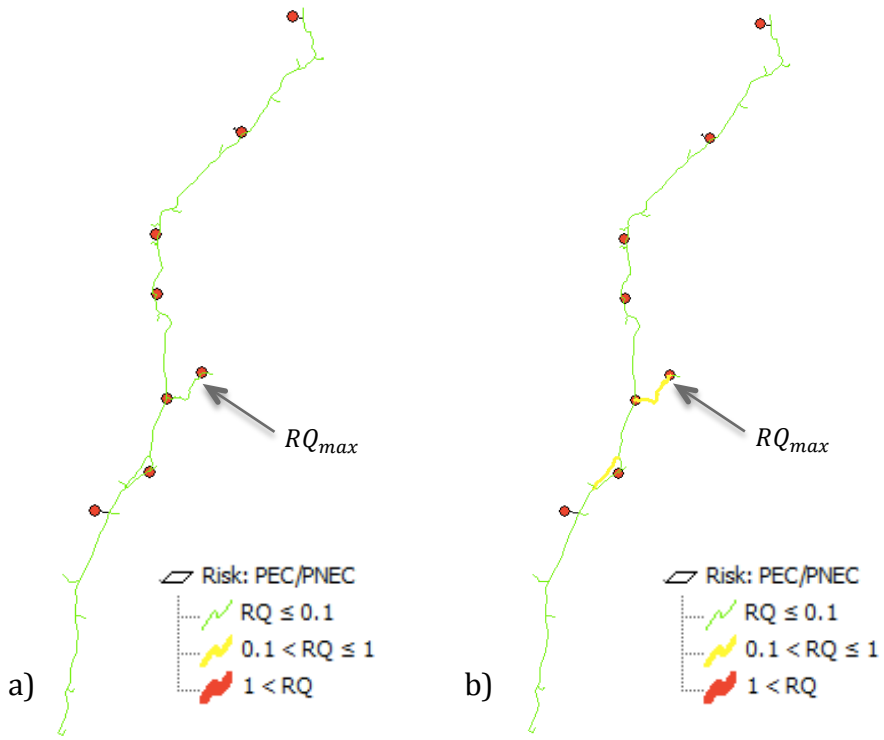


Figure 35: a) RQ for *Salmo salar* and *Salmo trutta* for diclofenac, propranolol, ethinylestradiol, ibuprofen, estradiol, paracetamol, sertraline, verapamil and estrone and the approximate location of RQ_{max}. b) RQ for *Salmo salar* and *Salmo trutta* for carbamazepine and the approximate location of RQ_{max}.

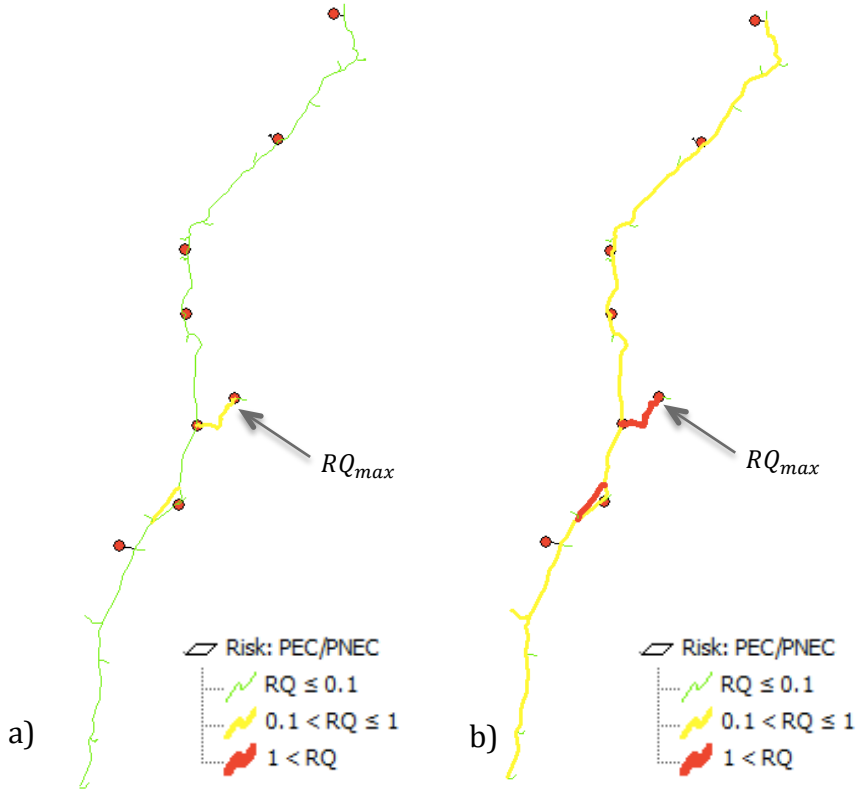


Figure 36: a) RQ for *Salmo salar* and *Salmo trutta* for metoprolol and the approximate location of RQ_{max}. b) RQ for *Salmo salar* and *Salmo trutta* for gemfibrozil and the approximate location of RQ_{max}.

4.3.2 Mixture effects

A geographically distribution of the calculated RQ for a mixture of the assessed pharmaceuticals is presented in Figure 37. The results for $RQ_{mix,CA}$ for *Salmo salar* and *Salmo trutta* is presented in the same figure for the two species since the results were quite similar. The values for $RQ_{mix,CA,max}$ were 11.46 and 11.40 for *Salmo salar* and *Salmo trutta* respectively, clearly exceeding one and therefore indicating that there is a risk for adverse effects in the parts of the Göta Älv river marked with red in Figure 37.

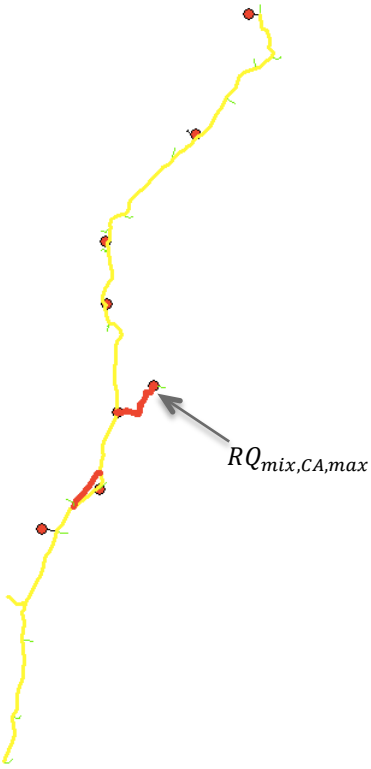


Figure 37: $RQ_{mix,CA}$ for *Salmo salar* and *Salmo trutta* in the Göta Älv river and the approximate location of $RQ_{mix,CA,max}$.

Almost all stretches marked with yellow in Figure 37 had values for $RQ_{mix,CA}$ close to one, and $RQ_{mix,CA}$ was higher than 1 for ten stretches. This implies that there might be a risk for adverse effects to *Salmo salar* and *Salmo trutta* in almost all stretches of the Göta Älv river when mixture effects are considered.

4.4 Habitat comparison

The results from the habitat comparison where the geographical distribution of known habitats of *Salmo salar* and *Salmo trutta* in the river (Figure 9) were compared with PECs and RQs for each pharmaceutical is presented in this section.

The colour-coded maps for all the studied pharmaceuticals, in section 4.1, with the geographical distribution of PECs in the Göta Älv river showed an increasing trend for PEC from Vänersborg and downstream the Göta Älv river, implying that the exposure generally is higher downstream the river. Therefore, fishes wandering from the ocean and upstream towards their spawning grounds will pass these parts of the river with higher exposure. The value for PEC_{max}, thus also the value for RQ_{max}, has the same location for all pharmaceuticals, that is after the Nygård WWTP that disharges into the tributary Gårdaån. In

Figure 9 it can be seen that there exist known habitats of *Salmo salar* and *Salmo trutta* in Gårdaån, but the tributary is not identified as an important spawning ground.

Considering individual effects

When Figure 35 b) and Figure 36 a) are compared with Figure 9 it can be seen that there are known fish habitats in the parts of the river with higher RQs. By comparing Figure 36 b) with the geographical distribution of known habitats of *Salmo salar* and *Salmo trutta* in Figure 9 it can be seen that there are known fish habitats where RQs became larger than one. More specifically, Solbergsån identified as an important spawning ground for the two fish species (Table 32 and Figure 9 b) reaches the Göta Älv river where the RQ was larger than one.

Considering mixture effects

Figure 37, showing the geographical distribution in the Göta Älv river of $RQ_{mix,CA}$ for *Salmo salar* and *Salmo trutta,* was compared with Figure 9, presenting the location of known habitats in the river. From this comparison it could be seen that there exist fish habitats where the $RQ_{mix,CA}$ is exceeding one.

4.5 Validation of the model results

The model results from GREAT-ER were validated by comparing modelled PECs with MECs in Swedish waters. Unfortunately, no studies with measured levels of pharmaceuticals in the Göta Älv river could be found, but instead MECs from studies performed for other Swedish waters were used (Table 33).

In the study by Fick et al. (2011), pharmaceuticals were detected in surface waters downstream the two WWTPs; Stadskvarn in Skövde and Kungsäng in Uppsala. The WWTPs discharge in small or moderately large rivers, and the dilution factors for Stadskvarn and Kungsäng WWTP are approx. two and 14 respectively. The dilution factor indicates how much the effluent from a WWTP is diluted in its recipient. Both Skövde and Kungsäng WWTP also receive waste water from hospitals, and therefore the surface waters samples taken downstream of these two WWTPs can be considered to be effluent-dominated according to Fick et al. (2011). In the year of 2010, when the samples were taken, Stadskvarn WWTP had 39 500 people connected (Miljörapport, 2010b) and Kungsäng WWTP had 160 200 people connected (Miljörapport, 2010a).

The comments in Table 33 indicate where the samples were taken. The samples in Fick et al. (2011) were taken 500 m downstream Stadskvarn WWTP and 3.5 km downstream Kungsäng WWTP. Two MECs, for propranolol and ethinylestradiol, are from recipients just specified as Swedish waters (SEPA, 2008). The MEC for gemfibrozil (Table 33) was measured about four km downstream Källby WWTP in the small Swedish river called Höje (Bendz et al., 2005). In the study by Bendz et al. (2005), a rough theoretical estimate of the concentrations of pharmaceuticals in the influent to the WWTP was done and then the number of people connected to the WWTP was assumed to be approx. 79 000.

Table 33: MECs in Swedish waters. LOQ is an abbreviation for the limit of quantification of the used analytical method in Fick et al. (2011).

Substance	MEC [ng/l]	Location of measurement	Reference
Diclofenac	21	Downstream Stadskvarn WWTP	Fick et al. (2011)
	28	Downstream Kungsäng WWTP	Fick et al. (2011)
Propranolol	0.2-2.1	In Swedish waters	SEPA (2008)
Carbamazepine	40	Downstream Stadskvarn WWTP	Fick et al. (2011)
	110	Downstream Kungsäng WWTP	Fick et al. (2011)
Ethinylestradiol	< LOQ	Downstream Stadskvarn and Kungsäng WWTP	Fick et al. (2011)
	< 0.05 - < 1	In Swedish waters	SEPA (2008)
Ibuprofen	36	Downstream Stadskvarn WWTP	Fick et al. (2011)
	69	Downstream Kungsäng WWTP	Fick et al. (2011)
Metoprolol	57	Downstream Stadskvarn WWTP	Fick et al. (2011)
	130	Downstream Kungsäng WWTP	Fick et al. (2011)
Gemfibrozil	70	Downstream Källby WWTP	Bendz et al. (2005)
Estradiol	< LOQ	Downstream Stadskvarn and Kungsäng WWTP	Fick et al. (2011)
Paracetamol (Acetaminophen)	100	Downstream Stadskvarn WWTP	Fick et al. (2011)
	37	Downstream Kungsäng WWTP	Fick et al. (2011)
Sertraline	< LOQ	Downstream Stadskvarn and Kungsäng WWTP	Fick et al. (2011)
Verapamil	< LOQ	Downstream Stadskvarn and Kungsäng WWTP	Fick et al. (2011)
Estrone	-	Not found for Swedish waters.	

The analytical method used in Fick et al. (2011) could not provide MECs for ethinylestradiol, estradiol, sertraline or verapamil probably because the limit of quantification (LOQ) for the analytical method was too high (10 ng/l). MEC for estrone in Swedish surface waters could not be found although estrone was analysed in several studies on Swedish waters (Fick et al., 2011; SEPA, 2008; Bendz et al., 2005; Andersson et al., 2006). MECs for estrone were, however, found for Korea and found to be 3.6-69.1 ng/l (Luo et al., 2014) and for the USA to be as high as 112 ng/l (Khanal et al., 2006). However, it is difficult to make proper comparisons with these MECs since they are not from Swedish waters.

The values for $PEC_{catchment}$ and PEC_{max} are generally much lower than the average MECs from the literature (Table 34). However, the PEC_{max} for propranolol and ethinylestradiol are similar to the MECs for some Swedish recipients (SEPA, 2008).

Table 34: Comparison of $PEC_{catchment}$ and PEC_{max} with average MECs from Swedish waters (Table 33). LOQ stands for limit of quantification for the used analytical method in Fick et al. (2011).

Substance	$PEC_{catchment}$ [ng/l]	PEC_{max} [ng/l]	Average MECs [ng/l]
Diclofenac	0.18	3.22	24.5
Propranolol	0.053	1.020	0.2-2.1
Carbamazepine	0.76	13	75
Ethinylestradiol	0.001	0.017	< 0.05 - < 1
Ibuprofen	0.48	7.09	52.5
Metoprolol	0.94	16	93.5
Gemfibrozil	0.2	3.78	70
Estradiol	0.0009	0.014	< LOQ
Paracetamol (Acetaminophen)	0.93	5.78	68.5
Sertraline	0.015	0.26	< LOQ
Verapamil	0.026	0.47	< LOQ
Estrone	0.0085	0.15	Not found

In order to evaluate the generally large difference between the values for $PEC_{catchment}$ and PEC_{max} and MECs, the dilution factors for the effluent from the WWTPs along the Göta Älv river were estimated. The estimated dilution factors for the WWTPs along the Göta Älv river were then compared to the dilution factors coupled to the different MECs in order to evaluate how comparable the PECs and MECs are (Table 34). The dilution factors were calculated by dividing the river flow with the effluent flow from each WWTP. The river flow at the location where the effluent from the WWTPs is discharged into the Göta Älv was used. The resulting dilution factors, presented in Table 35, are much larger than the ones for the effluent flows from the WWTPs in Fick et al. (2011). The effluent from Källby WWTP is discharged in a smaller river and therefore it can be assumed that the dilution factor is small as well. At the same time the number of people that are connected to the WWTPs along the Göta Älv river are also generally much less than for the WWTPs in the studies by Fick et al. (2011) and Bendz et al. (2005). The number of persons connected to the WWTPs along the Göta Älv can be seen in Table 17 in section 3.3.8. Because of the much higher dilution factors and less people connected to the WWTPs along the Göta Älv river, the comparability of the MECs and PECs (Table 34) can be questioned. However, it seems reasonable that the PECs from this study are lower than the MECs.

Table 35: Dilution factor for the effluent flow from the WWTPs. References for the effluent flow from each WWTP and a description for how the river flow was obtained is given in section 3.3.8.

WWTP	Effluent flow [m^3/day]	River flow [m^3/day]	Dilution factor
Vänersborg, Holmängen	13 282	51 840 000	3 903
Trollhättan, Arvidstorp	26 123	50 410 944	1 930
Hjärtum	96	51 639 552	537 912
Lilla Edet, Ellbo	2 015	52 186 464	25 899
Lödöse	434	51 840 000	119 447
Nygård	78	76 896	986
Älvängen	2 095	52 012 800	24 827
Diseröd	316	52 444 800	165 965

4.5.1 Comparing the results with PECs from a simple dilution model

In the study by Westerdahl (2009), PECs were calculated with a simple dilution model for the Göta Älv river for four different pharmaceuticals; diclofenac, propranolol, carbamazepine and ethinylestradiol. The PECs were calculated at 25 locations along the river. The simple dilution model includes hydrological data from SMHI and information about MECs of pharmaceuticals in WWTP effluents. The resulting PECs from the study by Westerdahl (2009) are presented in Table 36 together with the PECs from this study for the four pharmaceuticals.

Table 36: Comparison between PECs derived with a simple dilution model for the Göta Älv river (Westerdahl, 2009) and the PECs derived in this study from simulations with GREAT-ER.

Substance	PEC [ng/l] - simple dilution model (Westerdahl, 2009)	PEC_{max} [ng/l] – from this study simulated with GREAT-ER
Diclofenac	19 – 120	3.217
Propranolol	4.8 – 31	1.022
Carbamazepine	180 – 1 230	13
Ethinylestradiol	29 – 190	0.017

The simple dilution model predicts much higher concentrations than the ones obtained in this study. However, the simple dilution model does for example not include degradation of the pharmaceuticals in the river, which this study does.

4.6 Sensitivity and uncertainty analysis

Some discussions regarding the sensitivities and uncertainties of some input parameters and of the results are presented in this section.

4.6.1 The input parameters *k* and PNEC

The chronic PNECs, extrapolated from toxicity data with the aid of AFs, together with the in-stream removal rate *k* are two parameters identified to include large uncertainties in this study. Generally, the values for *k* or the half lives that *k* was calculated from were not reported from studies in similar climates as the one in Sweden. The environmental fate of pharmaceuticals in the aquatic environment is affected by temperature and pH for example. In countries with colder climate, like Sweden, the degradation is slower than in countries with warmer climate. Thus, the *k* values used in this study are probably overestimated.

The model results for RQ are quite sensitive to the chronic PNEC values. For example, if the PNEC values for carbamazepine and gemfibrozil were seen as chronic, then the RQs were smaller than one for the entire catchment. However, if the PNECs for carbamazepine and gemfibrozil instead were considered not to be chronic, implying that an AF of ten had to be used, the RQs became larger than one in some parts of the Göta Älv river. AFs should account for the uncertainties of applying the non-chronic toxicity data in a context were chronic effects are studied. The AF should also account for uncertainties of applying toxicity data for a certain species to another type of species. The answer to the question if toxicity data can be seen as chronic or not are perhaps not obvious and therefore this parameter includes a lot of uncertainty.

Another uncertainty in connection to PNEC is identified in the procedure of finding toxicity data. In this study, the possibility to see the toxicity data as chronic was evaluated after the lowest NOEC, or LOEC had been found. Perhaps toxicity data that can be seen as chronic, from long-term exposure studies, should have been prioritized already in the toxicity data selection step. At the same time, effort could have been put into finding toxicity data with perhaps more ecological relevant effect parameters like growth, behaviour, development and death rather than biochemical effect parameters. Although acute toxicity data were difficult to find for the assessment endpoints, the acute toxicity data that actually were found could have been used instead of in general choosing the lowest NOEC. Using the selection procedure described in this section could perhaps lead to different results compared to the ones obtained with the used procedure for finding chronic toxicity data in this study, see section 3.4.

4.6.2 Underestimated exposure

The exposure of pharmaceuticals in the Göta Älv river is probably underestimated in this study. This is because only overflows and treated flows at the WWTPs are included. There is a possible contribution to the concentration of pharmaceuticals in the river from overflows at main systems and pumping stations that have not been considered in this study. If more information could be obtained regarding overflows at the main system and at pumping stations these sources of pharmaceutical emissions into the river could be included in the model of the catchment. Neither have on-site sewage systems been considered nor overflows at the main system that transports waste water from for example the municipalities of Lilla Edet, Kungälv and Älvängen to Rya WWTP in Gothenburg. The fact that the exposure most

probably is underestimated has an implication. This is that perhaps there could be a risk for adverse chronic effects to the assessment endpoints in parts of the Göta Älv river for more pharmaceuticals than just gemfibrozil when they are considered individually.

4.6.3 Obtaining M from direct or backward calculation

Even if deriving *M* through backward calculation might not be the most straightforward alternative this solution has many advantages. Since an *M* derived by backward calculation is based on actual measurements of pharmaceuticals in Swedish WWTPs no consideration is needed for sale statistics of pharmaceuticals in Sweden. Information about neither the amount of pharmaceuticals that are bought but never used nor excretion rates of pharmaceuticals from the human body is needed. The backward calculation thus reduces the number of input parameters required. However, there are of course uncertainties coupled to measurement methods too. There may not be MECs available for the studied WWTPs and therefore MECs from other WWTPs have to be used, which was the case in this study. At the same time the measured data might perhaps not be representative for the exposure situation since they are done during a limited time, the measurements used in this study were from the year of 2008. Average values can be calculated from sale statistics. However, obtaining the value for *M* from backward calculation might still be preferable, especially if data required for direct calculation of *M* is missing for substances that are of interest to include in a study. That was particularly the case for ethinylestradiol and estrone in this study.

5 Conclusion

Concentrations of pharmaceuticals have been simulated in the Göta Älv river with the GREAT-ER model and mixture effects have been estimated using concentration addition as a conservative first tier. The results from this study indicates that there is a risk for adverse chronic effects from pharmaceuticals to fish like *Salmo salar* and *Salmo trutta* in the Göta Älv river when mixture effects are considered in a conservative first tier. The effect assessment considering individual pharmaceuticals only indicated that adverse chronic effects might occur for the pharmaceutical gemfibrozil. Thus the risk was underestimated when only individual effects were considered. However, the exposure of pharmaceuticals in the Göta Älv river is most probably underestimated in this study and the river flow in Gårdaån, where the maximum pharmaceutical concentrations were modelled, is overestimated. Therefore, there could be a risk for adverse chronic effects to the assessment endpoints in some parts of the river for more individual pharmaceuticals than just gemfibrozil. At the same time, there are uncertainties in the results for example arising from difficulties in finding chronic PNECs for the assessment endpoint of *Salmo salar* and *Salmo trutta*.

The study identified Gårdaån that is connected to Nygård WWTP and a part of the river close to Älvängen as the areas where the highest concentrations of pharmaceuticals were simulated. It can also be concluded that the conventional way of obtaining information about the quantity of emissions of pharmaceuticals through sale statistics are quite difficult. Missing data made it problematic to utilize this conventional way of obtaining information in this study. Therefore, obtaining data from measurements, if available, is a favourable option.

5.1 Suggestions for further studies

- Perform measurements of pharmaceuticals in the Göta Älv river
- A lot of more pharmaceuticals can be studied
- Include metabolites from pharmaceuticals
- Include more sources of emissions of pharmaceuticals
    - On-site sewage systems
    - Overflows at main systems and pumping stations that are connected to WWTPs
    - Overflows at the main system that leads waste water from municipalities located near the Göta Älv river to Rya WWTP in Gothenburg
    - Agricultural run-off (veterinary pharmaceuticals)
- Investigate mixture toxicity considering more pharmaceuticals
- Evaluate the requirement for higher tier mixture toxicity assessment

6 References

Aldekoa J, Medici C, Osorio V, et al. (2013) Modelling the emerging pollutant diclofenac with the GREAT-ER model: Application to the Llobregat River Basin. *Journal of Hazardous Materials* 263: 207-213.

Alder AC, Schaffner C, Majewsky M, et al. (2010) Fate of β-blocker human pharmaceuticals in surface water: Comparison of measured and simulated concentrations in the Glatt Valley Watershed, Switzerland. *Water Research* 44: 936-948.

Andersson J, Woldegiorgis A, Remberger M, et al. (2006) Results from the Swedish National Screening Programme 2005 Subreport 1: Antibiotics, Anti-inflammatory substances and Hormones.

Araujo L, Villa N, Camargo N, et al. (2011) Persistence of gemfibrozil, naproxen and mefenamic acid in natural waters. *Environmental Chemistry Letters* 9: 13-18.

Backhaus T and Faust M. (2012) Predictive environmental risk assessment of chemical mixtures: A conceptual framework. *Environmental Science and Technology* 46: 2564-2573.

Bendz D, Paxéus NA, Ginn TR, et al. (2005) Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden. *Journal of Hazardous Materials* 122: 195-204.

Boeije G. (1999) *GREAT-ER Technical Documentation - Chemical Fate Models*. Available at: http://great-er.org.acelis.net/files/techdoc_model.pdf [Accessed 2014-06-14].

Brooks B and Hugget D. (2012) Human Pharmaceuticals in the Environment. Current and Future Perspectives. In: Shugart LR (ed) *Emerging Topics in Ecotoxicology. Principles, Approuches and Perspectives.* Springer.

Burgman M. (2005) *Risks and Decisions for Conservation and Environmental Management,* New York: Cambriddge University Press.

Calabrese EJ and Baldwin LA. (1993) *Performing Ecological Risk Assessments*: LEWIS PUBLISHERS.

Calisto V and Esteves VI. (2009) Psychiatric pharmaceuticals in the environment. *Chemosphere* 77: 1257-1274.

Cefic-LRI. (2014) *(The European Chemical Industry Council - The Long-range Research Initiative) Cefic toolbox - GREAT-ER*. Available at: http://www.cefic-lri.org/lri-toolbox/great-er [Accessed 2014-01-31].

Cunningham VL, Binks SP and Olson MJ. (2009) Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. *Regulatory Toxicology and Pharmacology* 53: 39-45.

Cunningham VL, Perino C, D'Aco VJ, et al. (2010) Human health risk assessment of carbamazepine in surface waters of North America and Europe. *Regulatory Toxicology and Pharmacology* 56: 343-351.

EC. (2012) (European Comission) Proposal for a Directive of the european parliament and of the council - amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy.

ECHA. (2014) *(European Chemicals Agency) Understanding REACH*. Available at: http://echa.europa.eu/web/guest/regulations/reach/understanding-reach [Accessed 2014-06-01].

ECOTOX. (2014a) *(Ecotoxicology database) About ECOTOX*. Available at: http://cfpub.epa.gov/ecotox/help.cfm?sub=about [Accessed 2014-05-06].

ECOTOX. (2014b) *(Ecotoxicology database) ECOTOX effects index*. Available at: http://cfpub.epa.gov/ecotox/browse_index.cfm?sub=effects [Accessed 2014-05-21].
ECOTOX. (2014c) *(Ecotoxicology database) ECOTOX species index*. Available at: http://cfpub.epa.gov/ecotox/browse_index.cfm?sub=species [Accessed 2014-05-21].
ECOTOX. (2014d) *(Ecotoxicology database) Quick database query*. Available at: http://cfpub.epa.gov/ecotox/quick_query.htm [Accessed 2014-04-12].
FASS. (2014) *(Pharmaceutical Specialities in Sweden) Läkemedel och miljö (Eng. Pharmaceuticals and Environment)*. Available at: http://www.fass.se/LIF/healthcarefacts?1&docId=46900&userType=0 [Accessed 2014-02-05].
Ferrari B, Mons R, Vollat B, et al. (2004) Environmental risk assessment of six human pharmaceuticals: Are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? *Environmental Toxicology and Chemistry* 23: 1344-1354.
Fick J, Lindberg RH, Kaj L, et al. (2011) Results from the Swedish national Screening Programme 2010. *Subreport 3. Pharmaceuticals.*
Finnveden G and Moberg A. (2005) Environmental systems analysis tools - an overview. *Journal of Cleaner Production* 13 (12): p. 1165-1173.
GREAT-ER. (2014) *(Geo-referenced Regional Exposure Assessment Tool for European Rivers) What is GREAT-ER*. Available at: http://great-er.org.acelis.net/pages/GenericSubPage.cfm?pageId=31&parentPgId=2 [Accessed 2014-03-06].
GÄVVF. (2013) (Göta Älv Water Conservation alliance) Rapport avseende vattendragskontroll 2012 (Eng. Report regarding controll of watercourse 2012).
Göransson G, Larson M and Bendz D. (2013) Variation in turbidity with precipitation and flow in a regulated river system-river Göta Älv, SW Sweden. *Hydrology and Earth System Sciences* 17: 2529-2542.
Hannah R, D'Aco VJ, Anderson PD, et al. (2009) EXPOSURE ASSESSMENT OF 17 alpha-ETHINYLESTRADIOL IN SURFACE WATERS OF THE UNITED STATES AND EUROPE. *Environmental Toxicology and Chemistry* 28: 2725-2732.
Hüffmeyer N, Klasmeier J and Matthies M. (2009) Geo-referenced modeling of zinc concentrations in the Ruhr river basin (Germany) using the model GREAT-ER. *Science of the Total Environment* 407: 2296-2305.
Jjemba PK. (2006) Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. *Ecotoxicology and Environmental Safety* 63: 113-130.
Johnson AC, Dumont E, Williams RJ, et al. (2013) Do concentrations of ethinylestradiol, estradiol, and diclofenac in European rivers exceed proposed EU environmental quality standards? *Environmental Science and Technology* 47: 12297-12304.
Khanal SK, Xie B, Thompson ML, et al. (2006) Fate, transport and biodegradation of natural estrogens in the environment and engineered systems. *Environmental Science and Technology* 40: 6537-6546.
Kortenkamp A, Backhaus T and Faust M. (2009) *State of the Art Report on mixture Toxicity - Final Report*. Available at: http://ec.europa.eu/environment/chemicals/effects/pdf/report_mixture_toxicity.pdf [Accessed 2014-06-14].
Kummerer K. (2008) Pharmaceuticals in the Environment - Sources, Fate, Effects and Risks. Berlin Heidelberg: Springer
Lam MW, Young CJ, Brain RA, et al. (2004) Aquatic persistence of eight pharmaceuticals in a microcosm study. *Environmental Toxicology and Chemistry* 23: 1431-1440.

Lantmäteriet. (2014) *(Swedish mapping, cadastral and land registration authority) Koordinattransformation (Eng. Coordinate transformation)* Available at: http://www.lantmateriet.se/sv/Sjalvservice/Koordinattransformation/ [Accessed 2014-05-03].

Lienert J, Güdel K and Escher BI. (2007) Supporting information. Screening method for ecotoxicological hazard assessment of 42 pharmaceuticals considering human metabolism and excretory routes. *Environmental Science and Technology*.

Lunn G, Rhodes SW, Sansone EB, et al. (1994) Photolytic destruction and polymeric resin decontamination of aqueous solutions of pharmaceuticals. *Journal of Pharmaceutical Sciences* 83: 1289-1293.

Luo Y, Guo W, Ngo HH, et al. (2014) A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Science of the Total Environment* 473-474: 619-641.

Länsstyrelsen. (2014) *(County Administrative Board) Länsstyrelsens Webb-GIS - Informationskartan Västra Götaland (Eng. County Administrative Board Webb-GIS - Information map for Västra Götaland)*. Available at: http://ext-webbgis.lansstyrelsen.se/Vastragotaland/Infokartan/ [Accessed 2014-05-03].

Miljörapport. (2008a) Miljörapport 2008 Stadskvarns avloppsverk (Eng. Environmental report 2008 Stadskvarn WWTP). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2008b) Miljörapport Borås avloppsreningsverk, Gässlösa 2008 version 2 (Eng. Environmental report Borås, Gässlösa WWTP 2008 version 2). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2009) Miljörapport avloppsreningsverket Ryaverket 2008 version 1 (Eng. Environmental report Rya WWTP 2008 version 1). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2010a) Miljörapport 2010 Kungsängsverket (Eng. Environmental report 2010 Kungsäng WWTP). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2010b) Miljörapport 2010 Stadskvarns avloppsverk (Eng. Environmental report 2010 Stadskvarn WWTP). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2010c) Miljörapport 2010 Stockholm vatten (Eng. Environmental report 2010 Stockholm water). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2010d) Miljörapport Öns avloppsreningsverk år 2010 (Eng. Environmental report Ön WWTP year 2010). *Recieved via e-mail from Cecilia Niklasson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2013a) Miljörapport Diseröds avloppsreningsverk 2013 (Eng. Environmental report Diseröd WWTP 2013). *Recieved via e-mail from Mikaela Muñoz Eliasson (Projektledare VA-teknik) Municipality of Kungälv*.

Miljörapport. (2013b) Miljörapport Lilla Edet avloppsreningsverk 2013 version 1 (Eng. Environmental report Lilla Edet WWTP 2013 version 1). *Recieved via e-mail from Annika Svensson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.

Miljörapport. (2013c) Miljörapport Trollhättans avloppsreningsverk 2013 version 1 (Eng. Environmental report Trollhättans WWTP 2013 version 1). *Recieved via e-mail from Annika Svensson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.
Miljörapport. (2013d) Miljörapport Vänersborgs avloppsreningsverk 2013 version 1 (Eng. Environmental report Vänersborg WWTP 2013 version 1). *Recieved via e-mail from Annika Svensson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.
Miljörapport. (2013e) Miljörapport Älvängens avloppsreningsverk 2013 version 1 (Eng. Environmental report Älvängen WWTP 2013 version 1) *Recieved via e-mail from Annika Svensson, Division of Environmental Protection, County Administrative Board of Västra Götaland*.
Mårtensson A. (2014a) Engineer, municipality of Kungälv. Personal communication via e-mail. 2014-04-22.
Mårtensson T. (2014b) Driftcentralen Bispgården, Vattenfall Vattenkraft AB. Personal communication via e-mail. 2014-04-26.
NLM. (2014) *U.S. National library of medecine - ChemIDplus Advanced*. Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp [Accessed 2014-05-20].
PHYSPROP. (2014) *PHYSPROP database SRC inc*. Available at: http://www.srcinc.com/what-we-do/environmental/scientific-databases.html [Accessed 2014-05-20].
Price OR, Munday DK, Whelan MJ, et al. (2009) Data requirements of GREAT-ER: Modelling and validation using LAS in four UK catchments. *Environmental Pollution* 157: 2610-2616.
PubChem. (2014) PubChem Compound database. [Accessed 2014-05-07].
Rand GM. (1995) Fundamentals of aquatic toxicology. Effects, Envrionmental fate and Risk Assessment. Second edition. U.S.A: Taylor & Francis.
Rehnberg T. (2014) Investigator, the Swedish eHealth Agency. Personal communication via e-mail. 2014-05.
Schowanek D, Fox K, Holt M, et al. (2001) GREAT-ER: A new tool for management and risk assessment of chemicals in river basins contribution to GREAT-ER #10. 43: 179-185.
Schowanek D and Webb S. (2002) Exposure simulation for pharmaceuticals in European surface waters with GREAT-ER. *Toxicology Letters* 131: 39-50.
SEPA. (2008) *(Swedish Environmental Protetcion Agency) Avloppsreningsverkens förmåga att ta hand om läkemedelsrester och andra farliga ämnen (Eng. The ability of the waste water treatment plants to take care of pharmaceutical residues and other hazardous substances)*. Available at: http://www.naturvardsverket.se/Documents/publikationer/620-5794-7.pdf [Accessed 2014-02-05].
SMHI. (2014) *(Swedish Meteorological and Hydrological Institute) SMHI VattenWebb - Modelldata per område (Eng. SMHI WaterWebb - Modelled data per area)*. Available at: http://vattenweb.smhi.se/modelarea/ [Accessed 2014-05-03].
SMPA. (2013) *(Swedish Medical Products Agency) Läkemedelsboken 2014 - Läkemedel i miljön (Eng. Book of pharmaceuticals 2014 - Pharmaceuticals in the environment)*. Available at: http://www.l%C3%A4kemedelsboken.se [Accessed 2014-03-06].
Sumpter JP, Johnson AC, Williams RJ, et al. (2006) Modeling effects of mixtures of endocrine disrupting chemicals at the river catchment scale. *Environmental Science and Technology* 40: 5478-5489.
Sundberg R. (2014) Municipality of Ale. Personal communication. 2014-05-02.

Suter II GW. (2006) Ecological Risk Assessment. Second ed.: CRC press, Taylor & Francis group.
Svensson A. (2014) Environmental protection department, County of administrative board of Västra Götaland. Personal communication. 2014-04-10.
Trautwein C, Kümmerer K and Metzger JW. (2008) Aerobic biodegradability of the calcium channel antagonist verapamil and identification of a microbial dead-end transformation product studied by LC-MS/MS. *Chemosphere* 72: 442-450.
Vaj C, Barmaz S, Sørensen PB, et al. (2011) Assessing, mapping and validating site-specific ecotoxicological risk for pesticide mixtures: A case study for small scale hot spots in aquatic and terrestrial environments. *Ecotoxicology and Environmental Safety* 74: 2156-2166.
van Leeuwen CJ and Vermeire TG. (2007) Risk Assessment of Chemicals: An Introduction. 2nd edition ed. 2nd edition. Dordrecht, Netherlands: Springer.
VGR. (2008) (Region Västra Götaland) Läkemedels miljöpåverkan. Rapport - Kartläggning av läkemedelsrester i Västra Götaland (Eng. The Environmental influence of pharmaceuticals. Report - Mapping pharmaceutical residues in Västra Götaland).
Wagner J-O and Koorman F. (2011) GREAT-ER Desktop version 3.0 - GREAT-ER Desktop manual. Obtained from the GREAT-ER Desktop Version 3.0 CD ordered from http://great-er.org.acelis.net/pages/order.cfm [Accessed 2014-01-27].
Wagner J-O, Koorman F and Heinecke A. (2011) GREAT-ER Desktop Version 3.0 - Preprocessing manual. Obtained from the GREAT-ER Desktop Version 3.0 CD ordered from http://great-er.org.acelis.net/pages/order.cfm [Accessed 2014-01-27].
Westerdahl J. (2009) Ecological Risk Assessment of the River Basin of Göta Älv - A study according to the PETAR procedure. Göteborg: Chalmers University of Technology.
WHOCC. (2013) (World Health Organization Collaboring Centre) Guidelines for ATC classification and DDD assignment 2014. Oslo: WHO Collaborating Centre for Drug Statistics Methodology.
WHOCC. (2014) *(World Health Organization Collaboring Centre) ATC / DDD index 2014*. Available at: http://www.whocc.no/atc_ddd_index/ [Accessed 2014-04-12].
Wind T, Werner U, Jacob M, et al. (2004) Environmental concentrations of boron, LAS, EDTA, NTA and Triclosan simulated with GREAT-ER in the river Itter. *Chemosphere* 54: 1135-1144.
Åberg G. (2014) Municipality of Lilla Edet. Personal communication. 2014-04-16.
Årsrapport. (2013a) Årsrapport Hjärtum avloppsreningsverk 2013 (Eng. Annual report Hjärtum WWTP 2013). *Recieved via e-mail from Mikael Asplund. Municipality of Lilla Edet.*
Årsrapport. (2013b) Årsrapport Lödöse avloppsreningsverk 2013 (Eng. Annual report Lödöse WWTP 2013). *Recieved via e-mail from Mikael Asplund. Municipality of Lilla Edet.*
Årsrapport. (2013c) Årsrapport Nygård avloppsreningsverk 2013 (Eng. Annual report Nygård WWTP 2013). *Recieved via e-mail from Mikael Asplund. Municipality of Lilla Edet.*

7 Appendix

In this chapter, the information required to obtain *M* with forward calculation and the source files for GREAT-ER required to create the catchment of the Göta Älv river are described.

7.1 Information connected to the forward calculation of *M*

The ATC codes for the pharmaceuticals for which assigned DDDs were found (WHOCC, 2014) are given in Table 37.

Table 37: Pharmaceuticals with ATC codes that had assigned DDDs on the WHOCC webpage (WHOCC, 2014).

Substance	ATC code	Administration route	Assigned DDD	Unit for DDD
Diclofenac	M01AB05	O - oral solid	0.1	gram
	M01AB05	P - parenteral	0.1	gram
	M01AB05	R - rectal	0.1	gram
(diclofenac combinations)	M01AB55	O - oral solid	0.1	gram
Propranolol	C07AA05	O - oral solid	0.16	gram
	C07AA05	O - oral liquid	0.16	gram
Carbamazepine	N03AF01	O - oral solid	1	gram
	N03AF01	O - oral liquid	1	gram
	N03AF01	R - rectal	1	gram
Ethinylestradiol	G03CA01	O - oral	25	microgram
	L02AA03	O - oral	1.5	milligram
Ibuprofen	M01AE01	O - oral solid	1.2	gram
	M01AE01	O - oral liquid	1.2	gram
	M01AE01	R - rectal	1.2	gram
Metoprolol	C07AB02	O - oral solid	0.15	gram
Gemfibrozil	C10AB04	O - oral solid	1.2	gram
Estradiol	G03CA03	O - oral solid	2	milligram
	G03CA03	TD - transdermal	1	milligram
	G03CA03	V - vaginal	25	microgram
Paracetamol	N02BE01	O - oral solid	3	gram
	N02BE01	O - oral liquid	3	gram
	N02BE01	P - parenteral	3	gram
	N02BE01	R - rectal	3	gram
Sertraline	N06AB06	O - oral solid	50	milligram
	N06AB06	O - oral liquid	50	milligram
Verapamil	C08DA01	O - oral solid	0.24	gram
Estrone	G03CA07	O - oral	1	milligram

The sale statistics given in DDD/(1000 capita*year) for 2009-2013 in Västra Götaland obtained from the Swedish eHealth Agency via Rehnberg (2014) are presented in Table 38.

Table 38: Sale statistics from the Swedish eHealth Agency in DDD/(1000 capita*year) for 2009-2013 in Västra Götaland.

Substance	ATC code	Administration route	Sold DDD/(1000 inhabitants*year) 2009	2010	2011	2012	2013
Diclofenac	M01AB05	O - oral solid	4 690.54	4 701.35	4 706.93	4 597.82	4 047.67
	M01AB05	P - parenteral	0.24	0.31	0.19	0.21	0.15
	M01AB05	R - rectal	205.10	211.13	201.72	181.63	177.16
(diclofenac combinations)	M01AB55	O - oral solid	323.22	279.74	265.91	256.63	241.65
Propranolol	C07AA05	O - oral solid	778.23	761.21	772.75	768.52	772.40
	C07AA05	O - oral liquid	0.77	0.73	0.52	0.96	0.96
Carbamazepine	N03AF01	O - oral solid	768.80	747.50	735.69	713.69	701.74
	N03AF01	O - oral liquid	14.76	14.06	13.80	13.93	12.45
	N03AF01	R - rectal	0.50	0.50	0.19	0.07	0.19
Ethinylestradiol	G03CA01	O - oral	no data	no data	no data	no data	no data
	L02AA03	O - oral	no data	no data	no data	no data	no data
Ibuprofen	M01AE01	O - oral solid	7 921.88	6 571.87	6 333.49	6 248.27	5 938.77
	M01AE01	O - oral liquid	35.55	32.98	32.50	39.97	45.80
	M01AE01	R - rectal	16.99	14.64	16.41	16.26	14.80
Metoprolol	C07AB02	O - oral solid	9 426.93	9 308.04	9 289.48	9 213.18	9 189.72
Gemfibrozil	C10AB04	O - oral solid	204.16	185.83	168.07	150.50	138.16
Estradiol	G03CA03	O - oral solid	571.37	520.88	519.08	513.41	496.09
	G03CA03	TD - transdermal	504.10	488.45	476.60	465.34	482.15
	G03CA03	V - vaginal	1 777.83	1 767.73	1 140.77	1 008.86	1 037.61
Paracetamol	N02BE01	O - oral solid	14 307.36	13 042.85	12 891.77	13 260.28	13 581.40
	N02BE01	O - oral liquid	68.05	56.33	57.62	54.41	51.83
	N02BE01	P - parenteral	0.00	0.01	0.02	0.01	0.02
	N02BE01	R - rectal	92.67	81.45	80.06	72.49	67.06
Sertraline	N06AB06	O - oral solid	6 745.10	7 263.16	8 095.17	8 937.19	9 809.29
	N06AB06	O - oral liquid	8.73	6.91	7.79	7.21	6.33
Verapamil	C08DA01	O - oral solid	431.32	403.57	375.38	354.02	338.69
Estrone	G03CA07	O - oral	no data	no data	no data	no data	no data

In Table 39, the average sold pharmaceuticals in 2009-2013 for Västra Götaland in kg/(capita*year) are given per ATC code but also in total for a pharmaceutical.

Table 39: Average sold kg/(capita*year) per ATC code and total average sold kg/(capita*year) per substance in Västra Götaland in 2009-2013.

Substance	ATC code	Administration route	Average sold in 2009-2013 [kg/(capita*year)]	Total sold in 2009-2013 [kg/(capita*year)]
Diclofenac	M01AB05	O - oral solid	4.5E-04	5E-4
	M01AB05	P - parenteral	2.2E-08	
	M01AB05	R - rectal	1.95E-05	
(diclofenac combinations)	M01AB55	O - oral solid	2.7E-05	
Propranolol	C07AA05	O - oral solid	1.2E-04	1.2E-4
	C07AA05	O - oral liquid	1.3E-07	
Carbamazepine	N03AF01	O - oral solid	7.3E-4	7.5E-4
	N03AF01	O - oral liquid	1.4E-05	
	N03AF01	R - rectal	2.9E-07	
Ethinylestradiol	G03CA01	O - oral	No data	No data
	L02AA03	O - oral	No data	
Ibuprofen	M01AE01	O - oral solid	7.9E-3	8E-3
	M01AE01	O - oral liquid	4.5E-05	
	M01AE01	R - rectal	1.9E-05	
Metoprolol	C07AB02	O - oral solid	1.4E-3	1.4E-3
Gemfibrozil	C10AB04	O - oral solid	2E-4	2E-4
Estradiol	G03CA03	O - oral solid	1.0E-06	1.6E-06
	G03CA03	TD - transdermal	4.8E-07	
	G03CA03	V - vaginal	3.4E-08	
Paracetamol	N02BE01	O - oral solid	4E-2	4.1E-2
	N02BE01	O - oral liquid	1.7E-4	
	N02BE01	P - parenteral	3.8E-08	
	N02BE01	R - rectal	2.4E-4	
Sertraline	N06AB06	O - oral solid	4.1E-4	4.1E-4
	N06AB06	O - oral liquid	3.7E-07	
Verapamil	C08DA01	O - oral solid	9.1E-05	9.1E-05
Estrone	G03CA07	O - oral	No data	No data

The fractions of pharmaceuticals that are not metabolized in the human body are given in Table 40.

Table 40: The fraction in % of pharmaceuticals that are not metabolized in the human body.

Substance	f_{nm} [%]	Comment	Reference
Diclofenac	15		Jjemba (2006)
	9.5 (2-23)	weighted mean (lowest - highest)	Johnson et al. (2013)
	16 (6-26)		Lienert et al. (2007)
Propranolol	< 1		Ferrari et al. (2004)
	5 (2 - 9)	average (min - max)	Lienert et al. (2007)
Carbamazepine	1 - 2		Jjemba (2006)
Ethinylestradiol	40 (21-54)	weighted mean (lowest - highest)	Johnson et al. (2013)
	59 (40 - 77)	average (min - max)	Lienert et al. (2007)
Ibuprofen	1 – 8		Jjemba (2006)
	30 (11 - 47)	average (min - max)	Lienert et al. (2007)
Metoprolol	11 (5 - 15)	average (min - max)	Lienert et al. (2007)
Gemfibrozil	6 (6 - 6)	average (min - max)	Lienert et al. (2007)
Estradiol	3 - 10	Estradiol is a natural hormone and is excreted naturally by women. According to Johnson et al. (2013) are 3 to 10 % of a consumed estradiol pharmaceutical excreted	Johnson et al. (2013)
Paracetamol	< 5		Jjemba (2006)
(Acetaminophen)	4 (2 - 5)	average (min - max)	Lienert et al. (2007)
Sertraline	< 0.2		Calisto and Esteves (2009)
Verapamil	< 4		Jjemba (2006)
Estrone	Not found		

7.2 Source text files for GREAT-ER

The source text files that were developed by the author, pre-processed in the GREAT-ER pre-processing program and uploaded into GREAT-ER are presented in the following sections. All information in the source text files is not described, the source files are only presented in order to provide a basic understanding of their structure.

7.2.1 Info file: catchment.desc

```
# GENERAL INFORMATION FILE
# Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual

# ID              : the base name for the actual source files that are suffixed with .drn,
# .rna, .dsd, .cbp, .lks, .pic and . bgd
# NAME            : the name of the catchment (this is the name of the catchment in
# GREAT-ER)
# DESCRIPTION     : gives a short description of the catchment
# IN-VERSION      : defines the format for the catchment source files
# OUT-VERSION     : defines the output format

ID=GotaAlv
NAME=Catchment of the Gota Alv river
DESCRIPTION= The catchment of the Gota Alv river, situated in the county of Vastra
Gotaland in Sweden.
IN-VERSION=1.0
OUT-VERSION=2.0
```

7.2.2 Digital river network file: GotaAlv.drn

```
# DIGITAL RIVER NETWORK
# Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual

# The discharge outlet point coordinates are not specifically written into GREAT-ER in the
# discharge site data file. However, it is important that a stretch start with this point since
# the discharges are connected to the first point of a specified river stretch in the discharge
# site data text file.

# The format of this file: first is the ID of a stretch written.
# On the lines under the stretch ID follows coordinate pairs that describe that particular
stretch.
# StretchID
# x,y
# x,y
# and so on...
# StretchID
# x,y
# and so on...

# COORDINATES for the entire catchment

# The coordinates are in the coordinate system: SWEREF 99 TM N,E.
# (N,E)=(Y,X) that is the N-coordinate is the Y-coordinate and E-coordinate is the X-
coordinate.

1000
345500.21,6475222.43
345523.93,6474223.67
1
345523.93,6474223.67
345584.54,6473224.91
2
345584.54,6473224.91
345784.82,6472819.08
346156.39,6472724.21
346217,6472574
3
346217,6472574
346308.67,6472224.68
346456.25,6471845.2
346453.61,6471484.17
346393,6471247

[…]

113
320995.16,6402540.73
320630,6401732
114
```

321408.9,6402029.49
321090.03,6401602.58
320707.92,6401650.01
320630,6401732

7.2.3 River network attributes file: GotaAlv.rna

```
# RIVER NETWORK ATTRIBUTES
# Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual

# StretchID          : the ID of the stretch to which  the river network attribute data belongs
# Qmean [m^3/s]      : average flow
# Q5 [m^3/s]         : fifth percentile flow
# vmean [m/s]        : average velocity
# v5 [m/s]           : fifth percentile velocity
# RealLength [m]     : real length of the stretch
# depthmean [m]      : average depth of the stretch
# depth5 [m]         : fifth percentile of the depth
# Name               : a name of the segment, can be unnamed.

# The format of the file:
# StretchID, Qmean, Q5, vmean, v5, RealLength, depthmean, depth5, Name
# If no information is available for some parameter then nothing is written.

1000,600,302.65,,,1001.6,,,Unnamed
1,600,302.65,,,1000.6,,,Unnamed
2,600,302.65,,,1003.7,,,Unnamed
3,581.91,200.96,,,1378.7,,,Unnamed

[…]

113,196,91.465,,,891.6,,,Unnamed
114,28.6,8.3365,,,1028.7,,,Unnamed
```

7.2.4 Discharge site data file: GotaAlv.dsd

```
# DISCHARGE SITE DATA
# Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual

# ID                 : the unique ID of the disharge site
# X                  : the x-coordinate for the position of the actual plant
# Y                  : the y-coordinate for the position of the actual plant
# Pop                : the actual real population that is connected to the discharge site
# DWF [m^3/d]        : the dry whether flow, assume this is the minimum flow out of the
# plant
# Flow [m^3/d]       : the effluent flow from the plant, i.e. the flow leaving the plant and
# entering the river
# Type               : the type of plant, can choose between - PS (primary settler), AS
# (activated sludge), TS (trickling filter) and AS/TS.
# StretchID          : the stretch to which the plant is connected (the emissions from a
# discharge enters the river at the first point of this given stretch)
# Name               : the name of the discharge site (specified for orientation and
# interpretation purposes)
```

The format of the file:
Each line defines one discharge.
ID, X, Y, Pop, DWF, Flow, Type, StretchID, Name

1,344487,6474302,27443,6280,13282,PS,1, Vanersborgs avloppsreningsverk
2,339311,6462586,56573,7006,26123,PS,19, Trollhattan avloppsreninsgverk
3,330578.236,6452173.990,386,21.041,96,PS,36, Hjartum avloppsreningsverk
4,330658.48,6446148.43,5759,705.25,2015,PS,44, Lilla Edet avloppsreningsverk
5,331673.180,6435614.798,1311,107.28,434,PS,57, Lodose avloppsreningsverk
6,335238.268,6438243.864,415,31.89,78,PS,61, Nygards avloppsreningsverk
7,329968,6428164,6158,802,2095,PS,73, Alvangens avloppsreningsverk
8,324384.781,6424297,1200,110.6,316,PS,85, Diserods avloppsreningsverk

Assume that they are PS (In this study complexity mode 1 was used, therefore the information about the type is never used in GREAT-ER but must still be stated)

7.2.5 Catchment boundary polygon file: GotaAlv.cbp

CATCHMENT BOUNDARY POLYGON
Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual

The polygon is described linewise by singe coordinate pairs.
The polygon must be closed, which implies that the first and last coordinate pairs must be identical.

338548.44,6463050.95
338593.24,6462824.32
338377.15,6462898.11
338548.44,6463050.95

This must be included, therefore some points were chosen but the catchment boundary is
not visualized in this study.

7.2.6 Background data file: GotaAlv.bgd

BACKGROUND DATA
Background data can be included in order for the user of the GREAT-ER model to include
different geographical background information.

Do not include any background data

7.2.7 Lakes file: GotaAlv.lks

LAKES
Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual
This file lists all the stretches that actually are lakes.
(This file can be empty but must exist)

The format of this file:
StretchID
The ID of the stretches that actually are lakes, they are listed with one stretchID per line.

No stretches are actually lakes in the Gota Alv river and therefore this file is empty.

7.2.8 Pictures file: GotaAlv.pic

```
# PICTURES
# Based on the GREAT-ER Desktop Version 3.0 - Preprocessing manual
# This file specifies eventual available picture files and the location of these pictures in the
# catchment.
# (This file can be empty but must exist.)

# The format of this file:
# ID, X, Y, File, Name

# No pictures were included. Therefore this file was left empty.
```