Selective serotonin reuptake inhibitors in the Baltic Sea region

The effects of SSRI on teleost fish

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Abstract

Pharmaceuticals, enter the aquatic environments through sewage treatment plants and may affect fish. This examination paper is a literature study that focuses on Selective serotonin reuptake inhibitors, SSRIs, exposure and the impacts on teleosts in the Baltic Sea by assessment of peer-reviewed literature and material. Teleosts affected by exposure of these substances may demonstrate physiologically as well as behavioral alterations. These can be observed as alterations in aggression, boldness, mobility, growth, feeding rate or in endocrine processes. The potential of which SSRI may effect teleosts depends on the pH of the aquatic environment, temperature, other contaminants and the fat solubility of the substances. Some effects caused by SSRI exposure may elicit ecological impacts. These particularly concern changes and effects in terms of evasiveness, reproductive capacity and ability to find food as well as alterations of interspecificity. Even the balance between population density, individual fitness and by extension survival might be affected. Effects in interspecificity may potentially lead to local extinctions and changes in food webs. Furthermore, results demonstrated that when a substance is bioaccumulated and the teleosts are eaten by predators on higher trophic levels, marine ecosystems can also be affected. Moreover a conclusion could be drawn the level of concentration of SSRIs in the aquatic environment may be of less significance since teleosts have the potential to bioaccumulate SSRIs in tissue over time and in this sense concentrations may reach harmful levels that can cause physiological or behavioural alterations. Continuous studies should refer to chronic tests studies with focus on a field testing environment for understanding of natural conditions and exposure. Furthermore, studies on how ecosystems may be affected should be important to give an overview of the problem with SSRI exposure. As the Baltic Sea is a sensitive environment, studies should be made on species living in this environment.

Keywords

SSRI; Teleost; Physical effect; Behavioral effect; Ecological impact.

Abstrakt

Läkemedel, i akvatisk miljö, släpps ut via avloppsreningsverken och påverkar fiskar. Uppsatsen är en litteraturstudie av vetenskapligt granskat material, vilken avgränsas till SSRIs påverkan på teleoster i Östersjön. Teleoster påvisar fysiska- och betteendeförändringar då de exponeras för ämnena. Dessa kan förändra aggression, djärvhet, rörlighet, tillväxt, matningshastighet och/eller endokrina processer. Hur mycket av läkemedlet som teleosterna tar upp beror på havets pH, temperatur, andra föroreningar samt ämnets fettlöslighet. Några effekter orsakade av SSRI exponering kan ha en ekologisk påverkan. Dessa gäller särskilt förändringar och effekter vad gäller flyktförmåga, reproduktiv förmåga samt förmågan att hitta föda. Detta då det direkt eller indirekt påverkar samspelet mellan olika arter av teleoster eller deras föda. Även balansen mellan populationstäthet, individuell fitness och i förlängningen överlevnad skulle kunna tänkas påverkas. Effekter mellan olika arter inom samma område kan möjligen leda till lokal artdöd och förändringar i näringsväven.
Resultat påvisade att då SSRI bioackumuleras och teleosterna äts av predatorer på högre trofisk nivå, kan även marina ekosystem påverkas. Slutsats kunde dras att koncentrationen av SSRI i vattnet är inte av betydelse då teleosterna bioackumulerar ämnet under sin livstid och får därigenom höga koncentrationer i vävnaden. Vidare drogs slutsatserna att SSRI i akvatisk miljö påverkar teleoster i såväl beteende- och fysiologiska förändringar, arternas samspel i ett samhälle kan påverkas, arter kan försvinna vilket leder till en förändrad näringsväv och i sin tur ekosystem, speciellt då en nyckelart försvinner/förändras. I fortsatta studier bör det ses till kroniska test där olika substanser blandas. Vidare bör studier kring hur hela ekosystem kan påverkas vara av vikt för att ge en överblick över hur stort problemet är. Då Östersjön är ett känsligt hav bör studier läggas på arter levandes i denna miljön.

Definitions

Following below are short list of word used in this paper. Furthermore the meaning of this word as they are used in the paper are explained.

Keystone species (predator/prey) - A species that has significant effects on its surroundings, and holds a critical role within a ecosystem for the maintaining of the properties of other species.
Chiral substance - is a geometric property of a molecule. A chiral substance exists as two or more mirror images of the same molecules. These different forms of the same substance/molecule are called enantiomers. They are non-superimposable on each other. They may exhibit the same chemical properties, although their biochemical function may differentiate.
Racemic mixtures - same number of two enantiomers.
Enantiomer enriched mixtures - a purified (enriched) mixture containing a specific enantiomer of a substance.
Fitness - the properties of an organism that comprises its connection and relationship to the environment that effects the number of offspring and the population density of the organism's species.
Wild environment - the environment species naturally lives in.
Teleost - ray-finned fishes.
Non-target organism - an organism that was not planned to get effected.
Lipophilic properties - Non-polar substances that have a potential to be soluble in fat.
Cascade effect - the death of one species in an ecosystem triggers the extinction of other species.
Endpoint - a specific point of interests in experiments and studies to observe alterations and effects in a given situation. An example may be changes in behavior or biochemical processes after exposure to a specific substance.

Contents

1 Introduction

1.1 The Baltic Sea, a polluted brackish water system

The Baltic Sea is an extreme marine environment. It is geographically secluded and perifer to the rest of the world's oceans. The Baltic Sea has narrow and shallow bottlenecked sills at Öresund and Danish belts. It is an ecologically marginal environment due to its harsh physical conditions for ecosystems and marine life. Drastic changes and difference in temperature between annual seasons, a permanent low salinity, due to fresh water effluents and the brackish water of the Baltic Sea, are continuous stressors for marine life. The Baltic Sea is by its ecologically marginal environment low in species diversity, which in effect causes the marine ecosystems to be more sensitive. It would be difficult to save the ecosystem by introducing the same species from example the North Sea, since they do not have the genetics specifically developed by the individuals in the Baltic Sea through their isolation and the extreme conditions (Johannesson and André 2006; Sobek et al. 2016).

Furthermore the catchment area of the Baltic Sea densely populated with about 85 million inhabitants, in the nine countries surrounding the Baltic Sea, which continuously add anthropogenic stressors that can effect ecosystems (Sobek et al. 2016). Since the Baltic Sea is low in biodiversity it is therefore less resilient to added external stressors and pollutants, than other marine environments (Gunderson 2000; Sobek et al. 2016). The Baltic Sea is therefore polluted from anthropogenic sources. These pollutants or stressors are pharmaceuticals and their metabolites, industrial chemicals, heavy metals, pesticides and biocides from agriculture (Sobek et al. 2016; Magnusson and Norén 2012). Many of these compounds are toxic, bioaccumulative and persistent, they are found in concentrations in the environment proven to be toxic and hazardous to marine life and ecosystems. The water exchange rate for the Baltic Sea is very low, this in term causes a long retention time for persistent compounds present in the aquatic environment. This makes the Baltic Sea ecosystems more sensitive and vulnerable to volatile and hazardous pollutants than other marine environments (Sobek et al. 2016; Vieno et al. 2017).

1.2 Pharmaceuticals in the environment

Since pharmaceuticals for humans are designed to affect vertebrates and they later are able to reach the environment through waste water, It is important to look at the pharmaceuticals and the environment at large to understand how a single group of pharmaceutical substances can affect non-target organisms and aquatic environments (Fent, Weston and Caminada 2006; Brodin et al. 2014; Vieno et al. 2017).

WasteWater Treatment Plants, WWTPs, and Sewage Treatment Plants, STPs, in the countries in the catchment area of the Baltic Sea do not have the capacity and technology to eliminate SSRI and other pharmaceuticals completely thus they are found in sludge, effluent water and sediments in rivers and within the aquatic environment of the Baltic Sea (Johannesson and Andre 2006; Vieno et al. 2017).

Pharmaceuticals are designed to obtain specific biological effects and interact with physiological mechanisms at low concentrations. These effects can be manifested as behavioural, physiological and histological alterations. Furthermore pharmaceuticals are often designed to elicit effects over a period of time and not dissipate and leave the body altogether rapidly (Arnold et al. 2014; Kümmerer 2004; Huggett et al. 2003).

Pharmaceuticals, their residues and metabolites are derived from human or veterinary therapeutics. These compounds can be found in the environment by being discharged through treated municipal wastewater in WWTPs or STPs or by the overflowing of combined sewage (Vasskog et al. 2008; Glassmeyer et al. 2005; Richmond et al. 2016).

Depending on the physiological properties of a pharmaceutical, the substance is either metabolized or completely degraded, dissolved and partitioned in aqueous or solid phases, or to biosolids such as sewage sludge. They may even spread into the aquatic or terrestrial environments as earlier mentioned. Sometimes these compounds can, to some extent, be found in some or all of these alternatives (Arnold et al. 2014; Kümmerer 2004).

Pharmaceuticals are designed to be stable and resist human metabolism which lead to a low environmental degradation (Sebire et al. 2015). Pharmaceuticals designed to be nonpolar and through this they can pass freely by diffusion over biological barriers and membranes to target specific tissues, receptors and cells. The specific targets of pharmaceuticals and their diverse and complex structure enables the precise pharmaceutical selectivity processes. By this, it is reasonable to presume that since pharmaceuticals are designed to function and target specific biological targets, as enzymes, receptor systems, in one animal group, it will have similar effects in animal groups sharing this specific target mechanism. It is known that such targets for pharmaceuticals in mammals, are common amongst vertebrates and by this also in teleosts (Huggett et al. 2003; Corcoran, Winter and Tyler 2010).

Many pharmaceutical compounds are chiral and distributed as racemic or enantiomer enriched mixtures. Enantiomers of a pharmaceutical share the same identical molecular structure and formula, and elicit the same physiological and biochemical properties. They may however differentiate in the manner of bioavailability, potency, toxicity, and environmental fate due to the stereospecific nature of the biological targets (Brooks et al. 2003; Stanley et al. 2007).

Psychotropic drugs have the similarity to other pharmaceutical groups in the sense that they are not entirely degraded or metabolised in the human body. Some of these substances pass through the human body unchanged and others are only partially metabolized, and thus excreted as the unchanged compound or as the metabolites of the active pharmaceutical compound (Halling-Sørensen et al. 1998; Heberer 2002; Arnold et al. 2014; Brodin et al. 2014; Richards and Cole 2006).

The psychotropic drugs are partially or largely metabolised and broken down. They often continue through the WWTP to be biologically active and effect its surroundings and fish. In some cases these metabolites may be transformed into an earlier stage,

parent compound, through bacterial action and environmental conditions in the aquatic environment. In some cases, the metabolites rather than its parent compound may be more bioavailable, reactive and toxic to organisms. On other hand they may be reverted back to a more volatile and hazardous parent compound (Arnold et al. 2014; Halling-Sørensen et al. 1998; Richards and Cole 2006).

Pharmaceutical residues in aquatic environments can pose threats to aquatic organisms as well as ecosystems even if residues are not found in the tissues of the organisms. An example of this is exposure to relaxant stimulus drugs and painkillers. Exposed individuals can over-exert themselves in fights and chases and thus risk injuries, exhaustion and death (Arnold et al. 2014). Another example is the manner of exposure and the concentration of which teleosts are subjected to. Low concentrations but long-term exposure through continuous release of pharmaceuticals into the environment can result in chronic exposure, rather than direct acute exposure over a shorter period of time (Corcoran, Winter and Tyler 2010; Stanley et al. 2007). This due to the SSRIs ability to bioconcentrate and bioaccumulate which in term can increase the possibility of adverse and immense biological environmental effects (Corcoran, Winter and Tyler 2010).

Many pollutants and pharmaceuticals occurring in the aquatic environment can cause negative and disruptive effects on normal endocrine functions. Endocrine-disruptive and inhibiting agents main target is the central nervous system. Social behaviours under hormonal control such as dominance, aggression and activity may often be effected after exposure to such substances (Zala and Penn 2004). These behaviours are a key relationship between an organism and its surrounding environment (Little 2002).

Environmental screenings for pharmaceuticals in Sweden have identified substances and metabolites of analgesics, benzodiazepines, neuroleptics, atypical antipsychotics and SSRI pharmaceuticals. The reports present data from findings in samples of influent, effluent waters, sediment and sewage sludge from WWTPs, ss well as from drinking water samples (see table 1) (Fick et al. 2011; Woldegiorgis et al. 2007).

Table 1: Pharmaceuticals found in the aquatic environment in Sweden. The presented concentrations represent the highest measured values in the reports. * SSRI substances.

Pharmaceutical	Influent water / concentration (ng/L)	Effluent water / concentration (ng/L)	Drinking water / concentration (ng/L)	Biota / concentration (µg/kg)
Ibuprofen	1900	990	-	-
Carbamazepine	2600	1100	19	-
Paracetamol	540000	580	15	-
Diclofenac	7000	3900	140	-
Tramadol	6100	3000	-	-
Oxazepam	1800	730	14	9.6
Citalopram*	1000	480	6.6	-
Fluoxetine*	240	94	-	6.7
Sertraline*	160	32	-	14
Paroxetine*	130	44	-	17
Venflaxine	2200	700	8.6	-
Zolpidem	44	41	0.94	-
Buporpion	82	41	1	-
References: Woldegiorgis et al. 2007; Fick et al. 2011				

In the recent UNESCO and HELCOM report (Vieno et al. 2017) measurements and analytic data from across the entire Baltic Sea region have identified a presence of pharmaceuticals in the aquatic environment. The analysed data have been sampled from tissue, sediment, influent, effluent water and sewage sludge from WWTPs as well as water from rivers. The identified substances (see table 2) can be counted among pharmaceutical groups such as analgesics and anti-inflammatory agents, hormones and hormone antagonists, dermatological agents, chemotherapeutic agents and X-ray medias and central nervous system agents (such as psychotropic, antiepileptic and muscle relaxant pharmaceuticals). Furthermore the report presents the highest concentrations of psychotropic drugs in the Baltic Sea region to be detected along the entire Swedish east coast, outside of Germany's, Estonia's and Finland's coastal zones (Vieno et al. 2017).

Table 2: Pharmaceuticals identified within the Baltic Sea catchment area. Samples have been identified from water (sea water, influent/effluent from MWWTPs and rivers), sediment and biota. * SSRI substances.

Pharmaceutical	Water / concentration (µg/L)	Sediment / concentration (µg/kg d.w.)	Biota / concentration (µg/kg w.w)
Ibuprofen	0.158	45	2.4
Paracetamol	0.36	69	-
Diclofenac	0.054	3.5	5.2
Oxazepam	0.0019	-	6.7
Citalopram*	0.5	-	-
Fluoxetine*	0.1	-	4
Sertraline*	0.01	-	10
Paroxetine*	0.1	-	5
Venflaxine	0.001	-	-
Carbmazepine	0.033	-	141
17α-etynylestradiol	0.0011	-	-
Clofibric acid	0.0004	-	-
Reference: Vieno et al. 2017			

1.3 SSRI

Selective serotonin reuptake inhibitors, SSRI, is a term for a pharmaceutical group of substances that are mainly used to treat and alleviate anxiety, psychosis, depression, obsessive compulsive disorder, post-traumatic stress disorder, body dysmorphic disorder and sleeping disorder (Dorelle et al. 2017). Substances that belong to the pharmaceutical group SSRI are as following but not limited to: fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram (Hiemke and Härtter 2000). SSRIs are so called psychotropic pharmaceuticals which have been specifically designed to target and effect the neurochemistry in humans (Vega, Mortimer and Tyson 2003; Vasskog et al. 2008; Stanley et al. 2007).

The primary function of SSRIs is to block the reuptake of serotonin in the presynaptic nerve terminal, which causes the concentration of serotonin to increase in the synaptic cleft so called extracellular serotonin. For example patients with depression treated with SSRIs such as sertraline, may be alleviated and the treatment results in a better state of mind (Kitaichi et al. 2010). Furthermore patients treated with fluoxetine have displayed decreased appetite and aggression, why it can be prescribed as treatment for obsessive compulsive disorders and personality disorders (Brooks et al. 2003).

SSRIs as many other pharmaceuticals find their way into the environment either as the active compound or as its respective metabolites. Some of the metabolites might themselves be biologically active and potent, and may also display the same selective serotonin inhibiting effect as the parent compound. In this sense they may still be harmful in the environment as the parent compounds (Vasskog et al. 2008).

Many of the SSRIs are chiral substances. An example of this is fluoxetine. It exists as S-fluoxetine and R-fluoxetine. The demethylated metabolite S-norfluoxetine have been found to be more than 20 times more biologically activeness, and effective in its serotonin reuptake inhibiting properties (Heimke and Härtter 2000; Stanley et al. 2007). This when binding and targeting the specific serotonin receptors in organisms, than its enantiomer and mirror image counterpart, R-norfluoxetine, the metabolite of R-fluoxetine (Stanley et al. 2007).

The properties of the SSRI compounds make them lipophilic by nature and hence are the reason for their ability to bioaccumulate in tissue. Fluoxetine has the greatest potential to bioaccumulate in tissue and have been found to have the highest value for volume of distribution in tissue (see table 3) (Hiemke and Härtter 2000).

SSRIs have a long half-lifes to be pharmaceuticals, why the substance remains bioactive for a longer period of time. This property is what contributes to their persistence in the environment and in biological tissues until they are metabolised further into non-active compounds. Fluoxetine has the longest half-life of all SSRIs. Its demethylated metabolite S-norfluoxetine has an even longer half-life than the parent compound, and still rains the SSRI properties of its parent compound and remain bioactive (Hiemke and Härtter 2000) for more precise values for some SSRI substances please refer to table 3.

Table 3: The volume of distribution and half-life of SSRIs. This is the potential for the substance to bioaccumulate in tissue.

SSRI	Daily dose (mg)	Volume of distribution (L/kg)	Half-time	Metabolite	Halftime
Fluoxetine	20-80	20-45	1-4 days	Norfluoxetine	7-15 days
Sertraline	50-150	20	26hrs	N-desmethylsertraline	60-100hrs
Paroxetine	20-50	3-12	20hrs	-	-
Fluvoxamine	50-300	5	15hrs	-	-
Citalopram	10-60	14-16	36hrs	N-desmethylcitalopram	~2-3 times longer than halftime of citalopram
Source: (Hiemke and Härtter 2000)					

SSRI substances have been shown not only to effect the serotonergic system through serotonin reuptake and increase extracellular levels of serotonin, but also effect other endocrine signaling systems in the body, for example the noradrenaline reuptake inhibiting properties. Fluoxetine, sertraline and paroxetine have been shown to effect noradrenaline and dopamine extracellular levels in the prefrontal cortex of the brain (Hiemke and Härtter 2000; Kitaichi et al. 2010). Furthermore SSRIs have been observed to cause effects on other physiological functions and systems in organisms. It has been observed that effects may occur on the cardiovascular system, immune system and response, digestive process, endocrine system, secretion system, distortions of reproductive cells, the reproductive system, the behavioural systems and functions in teleosts (Dorelle et al. 2017; Kohlert et al. 2012; Stanley et al. 2007; Brooks et al. 2003; Perreault, Semsar and Godwin 2003; Menningen et al. 2009; Sebire et al. 2015; Lepage et al. 2005; Hiemke and Härtter 2000).

1.3.1 The occurance of SSRIs in the environment

The exact amount of SSRIs generally released into the aquatic environment is not fully known. Studies performed by the Swedish Environmental Institute from 2006 and 2010 found trace elements of SSRI compounds in, influent, and effluent waters as well as in dried sludge from STP. Some of these compounds could be measured in sewage sludge and some only detectable in aqueous phase due to the physiological properties of each substance or metabolite. Metabolites of SSRIs are more water-soluble, why they are more commonly found in water than in dry sludge. These substances could in a greater extent be identified in effluent waters from the STPs in the study. SSRI compounds such as fluoxetine, sertraline, paroxetine and citalopram have been identified through studies and screening programs in Sweden and around the whole Baltic Sea catchment area (Fick et al. 2011; Vieno et al. 2017; Woldegiorgis et al. 2007).

This is due to the lack of effective treatment methods for removing pharmaceutical compounds in STPs and WWTPs over the world in general. The majority of psychotropic drugs that are prescribed to patients are particularly persistent compounds that have the task of alleviating the patient and then quickly leaving the human body without decomposing why the active substance can be found in recipients from sewage treatment plants, either as parent compounds of metabolites (Brodin et al. 2014; Halling-Sørensen et al. 1998; Richards and Cole 2006).

In surface water samples as well as in aquatic organisms, the presence of SSRI substances has been found (Stanley et al. 2007). SSRI substances have been shown to elicit bioaccumulative properties. They have been identified in tissues from brain, liver, and muscles of teleost fish living in the vicinity of emission areas from effluent dominated streams in presence STPs (Brooks et al. 2005; Beyer and Meador 2011, 302).

1.4 Serotonergic system

The serotonergic system is based on the central nervous system adjacent to the raphne cells of the brain stem. This applies to both fish (Lillesaar 2011) and for larger vertebrates (Müller and Jacobs 2010, 51-64). There are some minor differences in the serotonergic system, but in terms of basic components and function, it is the same for all vertebrates (Gillette 2006).

Serotonin plays a major role in the central nervous system as it is a neurotransmitter that controls vertebrate behaviours like mood, sleep, appetite, aggression and learning. Serotonin is synthesized in the pineal gland, close to the two raphne centras in the innermost part of the teleost brain (Boyle 2005; Lillesaar 2011) It has been demonstrated that serotonin is involved in a range of psychological conditions such as depression, anxiety, obsessive compulsive disorder, eating disorder and addiction. In teleosts serotonin has a central function in mood, behaviours and stress, for domination and subordination (Winberg, Nilsson and Olsén 1992; Winberg and Lepage 1998; Dahlbom et al. 2012). Higher levels of serotonin concentration in teleosts and vertebrates have shown to be associated with a lower level of aggression and how feeding behaviour is regulated (Müller and Jacobs 2010, 23-24, 154; Veenstra-VanderWeele, Anderson and Cook 2000; Mohammad-Zadeh, Moses and Gwaltney-Bryant 2008; Lucki 1998; Lesch 2001; Perreault, Semsar and Godwin 2003; Bell et al. 2007; Dzieweczyński and Hebert 2012; De Pedro et al. 1998; Gaworecki and Klaine 2008; Mennigen et al. 2009; Hedgespeth, Nilsson and Berglund 2014; Voigt and Fink 2015).

Serotonergic activity has been shown to elicit effects on behaviours, this even through effects on other neurosignaling systems. Studies have found that interactions between serotonin and the arginine vasopressin signaling system may have effects on aggression (Perreault, Semsar and Godwin 2003). One of the main functions of SSRI is to effect the serotonergic system but is not alone in that regard. It has been demonstrated that in addition to pharmaceuticals other substances and compounds such as ammonia, metals and polychlorinated biphenyls may cause effects in the serotonergic system (Khan and Thomas 2000; Ortega, Renner and Bernier 2005; Menningen et al. 2009).

1.5 Effects induced by SSRI exposure

Physiological effects found through studies of SSRI exposure have ranged from effects on mobility, growth, fitness, reproductive cells and possible causing embryonic deformities. Physiological functions as immune response, thermal acclimation and mobility have also been proved to be effected by the presence of SSRI in teleost fish (Corcoran, Winter and Tyler 2010; Stanley et al. 2007; Foran et al. 2004).

Behavioural effects have also been elicited from SSRI exposure in teleosts. Effects have amongst several studies shown induced stress, altered feeding rate and feeding behaviours, decreased reproductional success, shelter seeking ability, courting behaviours and mobility (Corcoran, Winter and Tyler 2010).

Furthermore teleost fish effected by SSRI have demonstrated reduced altered social and aggressive behaviours. The ability perceives risks and predatory threats and to collaborate with conspecifics deteriorates after exposure to psychotropic pharmaceuticals such as SSRIs (Barry 2013; Stanley et al. 2007).

Ecological effects occur when a species is adversely effected, alternatively if its behaviours are changes so that it interferes with its function in the environment. If the density in a species population is changed, an entire food web in an ecosystem may change or be effected negatively (Corcoran, Winter and Tyler 2010; Brodin et al. 2014; Backhouse 2014).

1.6 Interspecies interactions and behaviours

SSRIs exposure may lead to changes in aquatic food chains and ecosystems under different environmental conditions. The aquatic environment and its organisms are effected by weather, temperature, pH, salinity, pollutants and pharmaceuticals as well as individual metabolism of the organisms (Corcoran, Winter and Tyler 2010; Schwaiger et al. 2014; Fent, Weston and Caminada 2006). A major threat to ecological interactions is altered behaviour patterns of one or more species in a food web (Werner and Peacor 2003). When an individual or a population of a species changes its behavioural patterns, other species are also effected. Since a food web is interconnected and species benefit from each other, and order in maintained by predator and prey relations there is a balance between the number of species and population size. Predators feed on species on lower trophic levels in the food chain that in turn feed on primary consumers. Since SSRIs are absorbed by aquatic organisms and bioaccumulated, seabirds, seals and vertebrates on higher trophic levels, which prey on those species, are also constantly exposed by the substances. SSRI are in other words bioaccumulated in tissue and biomagnified on higher trophic levels of the food chain. These substances can be bioaccumulated, be detrimental to physiological properties, and behaviours and thus may adversely effect one species function in a food web. By this, the interactions of the species with other species in the local ecosystem can be disturbed, and so the community structure and feeding relations (Vieno et al. 2017; Werner and Peacor 2003; Kohlert et al. 2012). An example of this is freshwater mussels, *Elliptio complanata*, that easily bioaccumulate fluoxetine, which are then eaten by a number of other vertebrate predators, and the substance thus follows with the food web upwards and may by extension effect land based vertebrates far from a SSRI contaminated aquatic environment (Arnold et al. 2014).

1.7 Biomarkers

A biomarkers is a biological, biochemical or physical measurable parameter, objectively measurable and quantifiable in studies. A biomarker makes it possible to determine exposure to substances that may cause alterations in physiological or behavioural processes. A biomarker can be measured as a biological entity that points to the presence or absence of a disease, a toxin, a biological state, a genetic pattern or therapeutic response to a certain pharmaceutical. In this sense biomarkers can be used to demonstrate that an effect is caused by exposure to a specific substance (Henderson 2017, 133-134; Handy, Galloway and Depledge 2003). An example of this is vitellogenin which is used as biomarker to reveal exposure to estrogenic compounds and substances. These can be natural and synthetic estrogenic substances as well as agricultural pesticides, polychlorinated biphenyls and surfactants (Pinto, Estêvão and Power 2014; Matozzo et al. 2008).

1.8 Purpose

The purpose of this examination paper was to acquire knowledge of how teleosts are effected by SSRI in the marine environment through review of scientific studies, peer-reviewed literature, articles, reports and publications. This is will be achieved by comparing and reviewing literature and source material, and to investigate what consequences for populations and ecological communities can be observed after exposure to these substances. Furthermore potential risks and future scenarios for aquatic ecosystems will be addressed.

1.9 Hypotheses

The hypothesis in this paper were: to demonstrate how teleost fish and ecosystems are effected by SSRI in the aquatic environment. To be able to reflect on how ecosystems are effected by SSRIs that enter the recipients from treated wastewater through WWTPs. The hope was to be able to demonstrate that the amount and concentration of SSRI found in water was inferior and of less relevance in that which it may effect teleost fish.

1.10 Problem statements

The following questions will be answered in this paper:
What are the effects from exposure of SSRI in teleosts?

Which are the effects and consequences in the aquatic environments effected by the presence of SSRI?

Can SSRI exposure effect interspecificity of teleosts?

Which are the potential future risks and possible long term scenarios for the aquatic ecosystems?

1.11 Delimitation

A delimitation in this paper will be made towards SSRI substances, an increasing prescribed group of pharmaceuticals, which have been detected in water recipients and studies indicate that SSRIs effect aquatic organisms (Corcoran, Winter and Tyler 2010; Brown et al. 2007). In regards to organisms of study a delimitation towards teleosts will be made. Teleost fish have developed spinal cords with bone marrow and detailed nervous systems, similarities to that of larger vertebrates. The nervous system and the brain of a teleost are similar to other vertebrates in basic components and function, although differing in complexity, size and form (Roberts 2012, 51-52) why they are an interesting focus for this paper.

A delimitation towards the Baltic Sea will be made in regards to its brackish water system with fresh water recipients. These systems are particularly interesting because brackish water systems tend to have a low exchange of waters, low circulation and salinity (Johannesson and André 2006; Sobek et al. 2016). These water systems and their ecosystems are low in diversity of species and species genetics, and may in this regard be more sensitive to drastic changes (Gunderson 2000).

2 Methods

Literature study methodology

The first and foremost method used in this examination paper is the form of a literature study. The main reason for this approach in this paper are that the main part of the knowledge in this field in found within peer-reviewed papers, articles, publications and reports. Moreover the timeframe for this paper is estimated not to accommodate the time required for any satisfying practical experiments. For the question formulations of this paper to be answered an overall literature study in deemed appropriate. To be able to answer the query about the mechanisms of exposure an information acquisition is suitable. To answer the last inquiry concerning consequences and effects in aquatic ecosystems, as well as to present potential future risks and scenarios a review and analysis of earlier studies, observations and experiments have been evaluated as appropriate approaches.

In this paper published relevant scientific source material has been evaluated, analysed, rewied and assed. Relevant search terms were used for gathering of literature and material through scientific databases, containing original copies of ecologic, toxicology and medical research articles, papers and publications. The university library was used for gathering information through printed books and specialist litterature.

Scientific databases used for the study presented in this paper are as the following: Science Direct, Scopus, ASFA, MEDLINE, OneSearch, Web of Science Core Collection, PubMed, as well as specialty literature within this field of study. Publications and journals used as source material in this paper are, but not limited to: Aquatic toxicology, Ecotoxicology, Toxicology Letters, Science, Chemosphere, Philosophical Transactions Of The Royal Society Of London Series B Biological Sciences, and the Handbook of the Behavioural Neurobiology of Serotonin. The literature that was not published specialty literature consisted mainly of scientific peer-reviewed articles, publications and reports. The methods and contents presented within the published source material have been scrutinised meticulously to be able to assess the value of its reliability and credibility. Each source material has been strictly evaluated and its respective relevance for this paper assed. Keywords used to find articles for this study: SSRI, fish, teleost, Baltic Sea, effects, behaviour, wastewater, aquatic environment, trait-mediated, aggression, ecotoxicology, drug interactions, and pharmacokinetics. The keywords have been combined in various constellations to produce connections to the peer-reviewed literature and material on which this examination paper is based.

The area of study that concerns this paper has a broad field of research, which consists of, but not limited to, studies on teleost fish. The part of this study that focuses on teleost fish is based on published research and experiments. The studies and experiments that form the foundation on which this paper is based are performed on teleost fish and vertebrates that are either exposed to or that previously was exposed to SSRI substances. These compounds have been measurable in tissue of these organisms.

To improve and complement this literature study a practical experiment and observations on teleost fish could have been made. This was however deselected since the timeframe for this study and paper was deemed insufficient for a practical experiment to me made in a satisfactory extent. Future research and studies within this field may perhaps demonstrate and establish how different species are effected by SSRIs, as non-target organisms, as well detect at what specific concentrations effects and alterations can be observed and measured in organisms. Areas that have not yet seen much attention and research are some of the organism's behavioural changes such as boldness and the ability to migrate. Future research into these areas can perhaps find how this effects the organisms and the ecosystems as a whole (Brodin et al. 2014).

The information acquisition for this paper is based on independent, validated and peer-reviewed why presented results and conclusions there of can be viewed as credible and convincing and representative. The literature that was selected has been validated and assessed compared to other published material, the publication date, the amount of citations have been used to assess the credibility and relevance of the literature. A number of authors and researcher are reoccurring in several articles that sometimes contradict each other. Therefore extra conscientiousness and time was invested in validating and assessing the credibility and relevance of this material. Altogether when referenced with studies and other independent sources the credibility can be deemed satisfactory. The information presented in this paper is considered sufficiently independent and verified to have results and conclusions drawn on reasonable and relevant grounds.

3 Results and discussion

3.1 Bioaccumulation of SSRI

The concentration of pharmaceutical substances and metabolites in aquatic environments is higher closer to the source of emission that has been identified in a recipient water system. If the level of pH in an aquatic environment is low, pharmaceuticals and metabolites have a larger potential for water solubility. This in term will make them more bioavailable to teleosts and more likely to be accumulated in tissue (Brooks et al. 2005; Vasskog et al. 2008; Fent, Weston and Caminada 2006) and pass over the gills (Brown et al. 2007). For teleosts to be able to absorb the substances through the cell membranes and bioaccumulate the substances in its tissues, the substances have to have lipophilic properties and be soluble in fat tissues, which SSRIs are (Heimke and Hertter 2000; Erb, Schappi and Rasenick 2016).

An contemporary problem is that aquatic non-target organisms are constantly exposed while human patients treated with the SSRI substances are exposed for a limited treatment time. This means that teleosts have been lifetime exposure from egg and spawn to adult individuals (Brown et al. 2007; Huggett et al. 2003; Fent, Weston and Caminada 2006). Many studies and experiments are performed as *In Vivo* tests, these studies are mostly focused on and limited to one substance in a closed test with clean water, while in the wild environment teleost are exposed continuously to numerous toxic and bioactive substances in their natural habitat (Brown et al. 2007). However, it has shown that it is of smaller consequence how high the concentration is for the influence of teleosts since they bioaccumulate SSRI (Kohlert et al. 2012). Some species take up and bioaccumulate more quickly than others, and are so affected more. however, considered that fluoxetine is an SSRI that is bioactive potent and easily absorbed and accumulated in tissue it has the conditions to cause major impacts on the fish (Kohlert et al. 2012; Lynn et al. 2007; Dzieweczynski and Hebert 2012). To what effect and degree teleosts are effected of the substance is dependant on the water temperature, they have been observed to intake less concentrations of substances through their gills, presumed due to a low metabolism, at lower temperatures (Brown et al. 2007). Since the Baltic Sea experience drastic changes in annual temperature this is of certain relevance for its aquatic environment and native teleost (Johannesson and André 2006). SSRI substances are designed to target specific receptors and proteins common amongst vertebrate species, there may be similar non-target effects found in fish exposed to these compounds (Stanley et al. 2007).

The studies found in the literature of which this paper is built have mostly been carried out over a certain period of time. To show effects in teleosts a certain time for exposure was required. If the dose and time in studies was too low, no effects could be found and studied. Furthermore the time and dose of exposure required to case effects and alterations in teleosts, difference between SSRI substance and teleost species (Stanley et al. 2007; Brooks et al. 2003; Brown et al. 2007; Sebire et al. 2015; Kohlert et al. 2012; Kitaichi et al. 2010). This have in turn demonstrated that certain species have easier to intake and bioaccumulate SSRIs. Other species need to be exposed for a longer period of time to bioaccumulate sufficiently high levels to affect the teleost physiologically or

behaviourally (Stanley et al. 2007; Lepage et al. 2005; Books et al. 2003; Foran et al. 2004; Sebire et al. 2015). Although the concentration of SSRIs in the aquatic environment is low, one can assume that a teleost over time can bioaccumulate a concentration harmful enough (Corcoran, Winter and Tyler 2010).

When different pharmaceutical compounds are found in the same environment, they can interact together to display and cause effects that are additive, non-additive and neutralizing of each other when in contact with organisms in an aquatic environment. It is difficult to rule out exactly how they may effect and interact with each other (Brodin et al. 2014; Altamura, Moro and Percudani 1994; Arnold et al. 2014; Backhouse 2014). An example of when substances are interacting with each other is citalopram combined in with 17α-ethinylestradiol, an endocrine disrupting pharmaceutical, tested on zebrafish, *Danio rerio.* The effects observed when the fish was exposed to environmentally low conditioning were that the effects of 17α-etynylestradiol were enhanced. Furthermore the fish indicated lower anxious behaviour when exposed to the two substances. Moreover this effect was differing when the fish were exposed to one of the two substances at a time. It is therefore important to understand the effects and biochemical mechanisms at work that may occur so that different substances are mixed and pollute the aquatic environment (Porseryd et al. 2017).

In order to identify where a cause of an certain effect comes from, or if it is caused by a particular substance, such as SSRIs, established biomarkers are required. Currently there are no identification of biomarkers connected to SSRI exposures, but are a subject that requires further research (Henderson 2017, 133-142). It is important that future research finds a biochemical mechanism to be able to demonstrate the effects, both physiological and behavioural alterations identified in organisms and to be able to tie them to a certain substance exposure (Handy, Galloway and Depledge 2003). When acute toxicity tests are carried out in clean tanks with a single substance, effects caused by this can be evaluated and observed, but biomarkers are needed in future to find out how SSRI affects the teleosts in nature. When this is established it may be possible to reveal if SSRIs behave as additive, non-additive or neutralizing pharmaceuticals when it comes to effects of exposure in nature. In this sense where they may interact with other substances in the aquatic environment (Arnold et al. 2014; Brodin et al. 2014; Handy, Galloway and Depledge 2003).

If the physical experiments and studies had been performed as field studies perhaps more reliable and interesting results may have been found. In this sense water containing a mixture of substances, pharmaceuticals, particles and pollutants, close to what can be observed in the wild environment, may interact and through this produce results close to natural exposure (Halling-Sørensen et al. 1998; Brown et al. 2007; Fent, Weston and Caminada 2006). But to be able to find decisive results and tie effects of exposure found in chronic exposure studies for SSRIs, biomarkers are needed to be defined for these substances.

3.2 Effects from exposure of SSRI in teleost

3.1.1 Physiological effects

Fathead minnow, *Pimephales promelas,* has demonstrated decreased growth and lower survival rates after exposure to the SSRI fluoxetine (Stanley et al. 2007). European perch, *Perca fluviatilis,* exposed to fluoxetine demonstrated decreased growth (Hedgespeth, Nilsson and Berglund 2016).

The endocrine function in fluoxetine-exposed Japanese medaka, *Oryzias laptipes,* has shown increased level of estrogen in females (Holmberg et al. 2011; Brooks et al. 2003). When exposed to fluoxetine they also displayed a decrease reproductive success and the number of eggs milted (see table 4). Of the eggs hatched, several fry had abnormalities such as curved spine, no pectoral fins, edema, reduced eyes and other malformations. This could in turn lead to decreased survival rate and alterations of populations density (Brooks et al. 2003; Foran et al. 2004).

Goldfish, *Carassius auratus,* have displayed decreasing milt release and an increase of gene expression for interstitial cell-stimulating hormone receptors (see table 4). Female fish exposed to fluoxetine demonstrated a decrease in food intake and decreased weight gain (Menningen et al. 2009).

Studies have shown that teleost exposed to pharmaceuticals such as SSRI, had a higher concentration of blood plasma, which also can be identified in human patients exposed to the same substance. From this, it can be concluded that some physiological effects the substance express in humans may also be applicable effects in aquatic organisms, especially teleost fish (Huggett et al. 2003; Valenti et al. 2012). All vertebrates have the same basic biochemical mechanisms and physiological processes why we can observe similar effects in teleosts as well as in other vertebrates (Huggett et al. 2003; Fent, Weston and Caminada 2006).

3.2.1 Behavioral effects

When SSRI substances reach non-target organisms in aquatic environments it can have profound consequences, such as induced stress, altered feed rate, feed behaviours, decreased reproduction success, shelter seeking, courting behaviours and mobility. The organisms become apathetic with disturbed mobility and do not perceive danger naturally as their evasive behaviours are diminished (Sebire et al. 2015; Stanley et al. 2007). These altered factors and behaviours, in turn, can affect the individual's and the species viability and reflects its fitness (Gaworecki and Kleine 2008).

It is crucial to distinguish between direct and indirect impacts of SSRI exposure. Direct impact effects leads to changes in physiological functions and behaviours of a species that affect their fitness (Stanley et al. 2007). Ecological effects may be able to occur when indirect impacts of SSRI exposure lead to changed behaviours leading to distorted species interactions especially when it comes to predation and competition. This causes

individuals to have an increased evasive and or hunting behaviour (Perreault, Semsar and Godwin 2003; Brooks et al. 2003).

Arabian killifish, *Aphanius dispar*, after exposed to fluoxetine the fishes has shown decreased swimming activity, social behaviour, chasing behaviour significantly (see table 4) (Barry 3013).

Siamese fighting fish, *Betta splendens,* is affected to a greater extent by the same concentration levels of a substance (Kohlert et al. 2012) than Rainbow trout, *Oncorhynchus mykiss*. Rainbow trout have been shown to be greatly sensitive to SSRI exposures, and it has been found to affect their natural feeding behaviours. SSRI can be prescribed to treat obesity and obsessive eating in human patients (Dorelle et al. 2017), when it comes to teleosts similarities between effected satiation and feeding behaviours can be observed (Winberg and Lepage 1998; Lepage et al. 2005; Holmberg et al. 2011). Fathead minnow has demonstrated decreased feeding behaviour after exposure to fluoxetine and lower survival rates (Stanley et al. 2007). When exposed to sertraline Fathead minnows displayed decreased boldness and reproductive behaviours (see table 4) (Valenti et al. 2012; Schultz et al. 2011).

Studies performed on Siamese fighting fish, exposed to sublethal levels of fluoxetine, which demonstrated decreased aggressive behaviour (see table 4). Siamese fighting fish males are selected in studies for their naturally aggressive and have a flamboyant fighting behaviour amongst conspecifics and to protect nest and territory. When exposed to fluoxetine the species have demonstrated a decrease in locomotor activity display of aggressive behaviours (see table 4). Already at low concentrations, much lower than what has been issued and classified as harmful and fatal concentrations of SSRI substances, their exposure have been proved to be able to effect the behaviour of the fishes. The study also found that the fishes' reaction time at a perceived threat was increased. Siamese fighting fish affected by SSRI have demonstrated reduced territorial aggression and locomotion activity (Kohlert et al. 2012; Lynn et al. 2007).

In rainbow trout, *Oncorhynchus mykiss,* citalopram have been found to decrease aggressive response and behaviours. The proportion of attacks in experiment environment as well as the dominance and appetite of the fish decreased considerably. A higher degree of inactivity when an intruder was introduced, to be another effect of exposure to the SSRI, citalopram (see table 4) (Lepage et al. 2005). In turn this may cause the exposed-individual to become easier prey for predators or to be chased from its territory by a dominant conspecific or by an intruding individual of another species (Hedgespeth, Nilsson and Berglund 2016; Werner and Peacor 2003).

Bluehead wrasses, *Thalassoma bifasciatum,* have a multiplex social system and have demonstrated decreased territorial aggression under influence of fluoxetine. The male fish lost their dominant and aggressive behaviours. The fluoxetine-exposed fish have shown altered social status among conspecifics due to modified behaviours (see table 4) (Perreault, Semsar and Godwin 2003).

Juvenile individuals of European perch exposed to fluoxetine showed decreased feeding rate and increased evasive behaviours. When exposed to sertraline, the fish displayed a increase in swimming activity as well as decreased shoaling tendency and feeding behaviours, and feeding rate even though this could not be proven with statistical credibility (Hedgespeth, Nilsson and Berglund 2016).

Furthermore Three-spined stickleback, *Gasterosteus aculeatus,* exposed to fluoxetine have displayed decreased threat response. SSRI-exposed male fish at all measured concentrations did exhibit inferior ability to build adequate nests (see table 4) (Sebire et al. 2015). When exposed to citalopram the individuals displayed a decreased food intake. This could be consider to that citalopram effect the nutrient intake in wild ecosystems (Kellner et al. 2015). During the spawning season, they become aggressive and exhibit increasingly territorial behaviours, why they are excellent when comparing and evaluating tests and studies in SSRI exposure (Kellner et al. 2015; Sebire et al. 2015), and to be able to imagine effects that could come to pass within aquatic enviroments in the Baltic Sea.

In table 4, a overview of species, some endpoints, concentrations and SSRI substances is presented to review how SSRI can effect some teleost species.

Table 4: Observed results by SSRI exposure in teleost fish. All concentration values are given in µg/L, if not otherwise stated.

Pharmaceutical	**Species**	**Endpoint**	**Concentration, µg/L**	**Reference**
Citalopram	Rainbow trout, *Oncorhynchus mykiss*	Aggression, mobility	100 µg/kg	Lepage et al. 2005
Fluoxetine	Arabian killifish, *Aphanius dispar*	Aggression, swimming activity, social behaviour	0.3	Barry 2013
Fluoxetine	Three-spined stickleback, *Gasterosteus aculeatus*	Nest building/quality	3.2-32	Sebire et al. 2015
Fluoxetine	Three-spined stickleback, *Gasterosteus aculeatus*	Threat response	32	Sebire et al. 2015
Fluoxetine	Siamese fighting fish, *Betta splendens*	Activity, aggression	3000	Lynn et al. 2007
Fluoxetine	Siamese fighting fish, *Betta splendens*	Activity, aggression	350	Kohlert et al. 2012
Fluoxetine	Siamese fighting fish, *Betta splendens*	Aggression	0.008-0.5	Dzieweczynski and Hebert 2012
Fluoxetine	Goldfish, *Carassius auratus*	Feeding rate	54 000	Mennigen et al. 2010
Fluoxetine	Goldfish, *Carassius auratus*	Decreased milt release, increase of geneexpression for luteinising hormone receptors	0.54	Mennigen et al. 2010
Fluoxetine	Bluehead Wrasses, *Thalassoma bifasciatum*	Aggression, social behaviour	6000 µg/kg	Perreault, Semsar and Godwin 2003
Fluoxetine	Fathead minnow, *Phimephales promelas*	Feeding rate	3.7	Stanley et al. 2007
Fluoxetine	Japanese medaka, *Oryzias laptipes*	Developmental abnormalities, repoductive sucess	0.1-5.0	Brooks et al. 2003
S-Fluoxetine	Fathead minnow, *Phimephales promelas*	Growth, feeding rate	51	Stanley et al. 2007
Sertraline	Fathead minnow, *Phimephales promelas*	Reproductive bahviour	0.0052	Schultz et al. 2011
Sertraline	Fathead minnow, *Phimephales promelas*	Boldness	3	Valenti et al. 2012
Sertraline	Fathead minnow, *Phimephales promelas*	Feeding rate	89	Hedgespeth, Nilsson and Berglund 2014

3.3 Effects in the aquatic environment

SSRIs are designed to target specific metabolic and molecular pathways, enzymes and proteins when treating human patients. These effects are possible because some animal groups, as teleost fish, share the same biological characteristics and targets, that SSRIs binds to, as humans. It is therefore of great importance that even in lower vertebrates as teleosts, it is thoroughly examined and analysed how they are effected by exposure by these compounds. It has been demonstrated that even at low concentrations fish may be affected due to chronic lifetime exposures, bioconcentration and bioaccumulation properties of SSRIs. If a species of teleosts are severely affected and their behaviours altered this may effect and threaten the aquatic ecosystem and food web stability and

function as a whole (Werner and Peacor 2003; Huggett et al. 2003: Hiemke and Härtter 2000; Fent, Weston and Caminada 2006; Corcoran, Winter and Tyler 2010).

Behaviours that could have direct ecological effects are feeding rate, predator avoidance, mating success, parental care and nest building. Moreover disturbances and changes in these behaviours may have a profound effect on reduced individual fitness, food intake and general growth (Brodin et al. 2014; Gaworecki and Kleine 2008). Changes in behaviours due to the exposure to SSRI, as fluoxetine, and its metabolites can have ecological impacts. This is because species behaviours are directly linked to individual fitness and population persistence. For example, how boldness responds to anti-predator response and how well the individual perceives threat and predators avoidance may result in reduced ability of shoaling cooperation (Gaworecki and Kleine 2008; Sebire et al. 2015). The changes in behaviours of the teleosts can affect their fitness, the population dynamics and ecosystem functioning (Werner and Pecaor 2003).

Individual behavioural changes like trade-offs, for example, to eat or being eaten, may result in alterations of population density, in form of increase, decrease or local extinction (Werner and Peacor 2003; Balvanera et al. 2006). If a species are locally extinct or population density altered, this may lead to a cascade effect throughout the food web in the ecosystem. If a species population on a higher trophic level, experiencing drastic changes in density will result in alterations in community composition and biodiversity which in term can impact ecosystem functioning (Ballinger and Lake 2006; Kidd et al. 2014; Gaworecki and Kleine 2008). If both predator and prey are effected and their behavioural patterns is altered the balance of the food web may be jeopardized, as each species is interlinked in a food web, they are affected by changes in another species population dynamics and key behaviours, as well as in the interactions with the other species, this may cause changes to the structure of the food web and aquatic ecosystem (Werner and Peacor 2003).

Behavioural effects and changes due to exposure to pharmaceuticals in the aquatic environment is of great ecological importance, since behaviour and fitness are paramount for the stability of a population, and in turn for the ecosystem (Brodin et al. 2014; Stanley et al. 2007).

3.4 Alterations of interspecificity induced SSRI exposure

If a species in an ecosystem is not itself sensitive to exposure of a pharmaceutical substance, its population can be significantly affected if its primary prey species would be effected and locally extinct from the exposure (Arnold et al. 2014). If one species are affected on its traits and severely compromised it could threaten an entire population and food web, in turn this can have effects over a whole ecosystem (Stanley et al. 2007; Arnold et al. 2014).
If predator-prey relationships and behaviours are altered intervening species populations will increase. If a species on a higher trophic level are locally extinct their main pray, for example phytoplankton density may increase. If biomass species are left unchecked by keystone predators the population may increase at rapid speeds causing too many consumers (Hedgespeth, Nilsson and Berglund 2016).

The Baltic Sea is a sensitive marginal ecosystem (Johannesson and André 2006). If further discharges of pharmaceuticals and mainly SSRI substances the consequences could be catastrophic. The behavioural and physiological changes, endangering interspecies interactions and functions (Arnold et al. 2014; Stanley et al. 2007; Hedgespeth, Nilsson and Berglund 2014), caused by these substances may in the long term lead to species extinctions, cascade effects up and down the food web of an ecosystem (Werner and Peacor 2003).

A decreased hunting behaviour, may in turn result in reduced instinct to find food for an organism. This may be concluded to result an impaired condition and viability of individuals in an effected species, which in itself can be theorized to effect an entire ecosystem. Changes and disturbances in natural colonizing, immigration and emigration behaviours of non-target organisms in aquatic environments and within populations are critical effects of fluoxetine exposure for aquatic organisms. A troublesome effect these substances have on fish living in shoals is disruptions and loss of cooperative behaviours and functions. Many species that living in shoals confuse the predator by working together. This ability deteriorates after the influence of fluoxetine substances, which makes the fish easier prey for predators. Behavioural changes such as these cause both individual and population pressures, as well as problems throughout an ecosystem (Hedgespeth, Nilsson and Berglund 2016; Hedgespeth, Nilsson and Berglund 2014).

3.5 Future risks and possible scenarios for aquatic ecosystems

In an ecosystem, organisms of different sizes and levels live in a food web why a local extinction or ecological death of a species can have devastating consequences. Trait changes in one species have been found to be interacting with food web and community properties. This can be understood through that individual species with altered behavioural patterns and interactions with conspecifics and other species effect population dynamics and food web function. If a keystone species is substantially affected, it would have a faster and more devastating process. It is primarily the higher trophic species, the keystone species, in a food web which becomes the most detrimental, which can lead to the keystone predator effect (Werner and Peacor 2003). When studying effects it should therefore be of significant value to look at several species within a food web and in the same ecosystem. This to be able to evaluate possible effects whilst simultaneously observing how they interact with each other after SSRI exposure have been identified in the environment. Especially when studying the species and effects of SSRI exposure within the Baltic Sea. The Baltic Sea is with its low biodiversity a sensitive and stressed environment why it is of dire importance to have this approach when assessing studies and analysing measured results. A complex ecological community in food webs can be affected by indirect interactions due to changes in density of intervening species. Trophic cascades and alterations of keystone predators population are a consequence of changes in population density of intervening species (Werner and Peacor 2003; Johanneson and André 2006).

The results indicate that environmental exposures for aquatic organisms is more complex than a study in clean water aquarium environments where a single psychotropic substance are introduced and then its effects studied on the test subjects (Brown et al. 2007). In the natural aquatic environment factors such as exposure to

concentrations over time, temperature, surfactants, suspended solids, colloids and other pharmaceuticals that may interact with pharmaceuticals, why this be taken into account, when assessing the effects on aquatic environments and teleosts (Schwaiger et al. 2004; Triebskorn et al. 2004; Mimeault et al. 2005). As the Baltic Sea is a marginal environment (Johannesson and André 2006) and several of discussed above factors exist in the natural environment, it should be taken into account.

When teleost bioaccumulates SSRIs in its tissue, predators on higher trophic levels might feed on the teleosts. Through this predator-prey interaction the predators can accumulate the substance the prey had bioconcentration in its tissue. It might therefore also affect land-based ecosystems since the food webs can me interconnected with aquatic ecosystems. An example of this can be seals and birds which would be affected by feeding on SSRI-exposed teleost fish (Werner and Peacor 2003; Kohlert et al. 2012; Hedgespeth, Nilsson and Berglund 2016).

The entire food web can be altered due to the fact that species affected by pharmaceuticals may display altered feeding behaviours (Brodin et al. 2014). If an individual teleost displays increased territorial behaviours and thus chasing after rival species or conspecific individuals. This may in turn cause the entire food chain within the ecosystem to be damage, and result in one or several species are extinct (Werner and Peacor 2003).

Few studies on species living in brackish water environments have been carried out, so the conclusion in this paper is drawn that teleost in these environments are effected similar to those studied in other aquatic environments. One species that can be coupled with brackish water and the Baltic Sea is specially the species three-spined stickleback (Kellner et al. 2015), which seem to react similar to SSRI exposure as other teleost. However, consideration must be given to the comparison that the Baltic Sea has a cooler temperature than other of the world oceans which can lead to a slightly smaller uptake (Johannesson and André 2006; Vieno et al. 2017). A low concentration and exposure over a long time can produce greater effects than a high concentration with a short time of exposure. This especially in regard to the bioaccumulative properties of SSRIs. Hereafter it is reasonable to conclude that the teleost are affected and, in itself, the ecosystem and food webs of the aquatic environments, although there may be some variation between the effects on different species. If one species behavioural traits and patterns are altered this in turn will affect the food web at large (Werner and Peacor 2003; Corcoran, Winter and Tyler 2010).

3.6 Future research

When pharmaceuticals that are chiral substances are prescribed to human patients, it is often administered as a racemic mixture of both chiral molecules. If more efforts were made into enriching a pharmaceutical with the more potent and biologically active enantiomer and by extension metabolite, perhaps less medication is needed which would be better for the environment (Stanley et al. 2007). This could possibly in the long term effect the aquatic ecosystems.

It may be wise to ensure physical experiments made in closed aquarium environments to study how a specific relevant substance and how it specifically effect a certain species, but to keep in mind that the mixture of pharmaceuticals can occur and interact in the wild environment (Schwaiger et al. 2004; Triebskorn et al. 2004; Mimeault et al. 2005). Therefore, more research into how mixed pharmaceuticals in the aquatic environments and how they may interact with each other and SSRIs are recommended. In these studies perhaps test subjects can be exposed to mixture of pharmaceuticals, substances and particles found in natural environments for evaluation and simulation of effects that may occur. In other words a field study of exposure and effects in teleosts. Since such kind of experiments hopefully can provide more accurate results and reliable conclusions and through that provide deeper and basic understanding into how a mixture of pharmaceutical substances interact and may effect aquatic life (Brown et al. 2007).

SSRI as a pharmaceutical group can effect and alter behaviour and physiology of a target organism. The fitness in an ecological sense must be taken into consideration during tests, as one of the main side effects of SSRI is apathy, growth, mass and body conditions as well as decreased feeding rate and libido (Werner and Peacor 2003; Sobek et al. 2016; Gaworecki and Kleine 2008; Little 2002; Stanley et al. 2007; Brooks et al. 2003). Furthermore experiments and studies should be carried out on defined behavioural endpoints tied to wildlife exposure and species interactions to demonstrate any ecological effects that might be observed (Brodin et al. 2014**)**. Moreover, increased efforts and research in understanding how SSRI exposure may challenge the individual fitness of a teleost species is needed. This may demonstrate how population dynamics may be impacted by alterations in species fitness. In addition focus on relevant chronic life-cycle studies should be made to better assess the effects of SSRI exposure in the aquatic environment (Brooks et al. 2003; Werner and Peacor 2003). Parallels might be able to show how ecosystems may be able to cope with further external, long term multiple substance exposure and other stressors.

For future research, all tests performed should include several substances in the wild environment where pharmaceutical substances, heavy metals and suspended particles can interact, which in term will effects how a pharmaceutical may act and its potential to interact with and affect organisms in the aquatic environment. The results should be more credible if they can be built from studies and experiments on the conditions in the wild aquatic environment (Halling-Sørensen et al. 1998; Brown et al. 2007).

The traits that may be altered in a food web depends on the species that would be exposed, time period of exposure, behaviour on a physiological within the specific species, involved substances or pollutants (Arnold et al. 2014). As mentioned earlier the Baltic Sea is a marginal environment and ecosystem with low species diversity with low genetic diversity within the species. This must be taken into account in future studies. This effects the resilience of the species and ecosystem and added pressure from stressors is taxing on stability (Johannesson and André 2006; Fent, Weston and Caminada 2006).

Furthermore areas that have not yet been studied in detail are the boldness of organisms and the ability to migrate (Halling-Sørensen et al. 1998; Brodin et al. 2014; Stanley et al. 2007). This may be important as such behaviour might the concluded to have ecological effects within the aquatic environment.

Moreover pharmacokinetics and pharmacodynamics of pharmaceuticals which find their way into the environment are fields of uncertainties that should be studied and researched more thoroughly in the future (Arnold et al. 2014). The interactions that SSRI and pharmaceuticals may have on behavioural and physiological functions must be better understood.

In addition the focus of the present research may be towards the toxicological aspects of a pharmaceutical, why their ability to alter and disrupts behavioural endpoints must be better understood and examined (Hiemke and Härtter 2000; Altamura, Moro and Percudani 1994; Brodin et al. 2014). Behavioural changes may have profound effects on a species ecological fitness, survival and function in the aquatic environment (Gaworecki and Kleine 2008; Little 2002).

To determine the effects of releasing a particular substance into nature, biomarkers is needed to link the effects in teleosts with a certain pharmaceutical exposure. In this way, the effects of pharmaceutical usage are linked to effects observed in the environment. Thus, it can be demonstrated how harmful a substance's effect in nature is and why its usage should be restricted and regulated, as it has become for antibiotics. Such research is needed in future studies to take biomarkers from laboration studies out into the wild. This would be a good way to prove what causes observed effects in field testing. If evidence of the effects is not demonstrated, it becomes difficult to prove that a substance must be used with greater caution in the future.

4 Summary and conclusions

In summary, it is reproductive behaviours, interactions between individuals, evasive and hunting, as well as feeding behaviours that are effected by exposure to SSRIs. This in term might lead to decreasing population density. The effects primarily effect the species negatively, which probably can have devastating consequences for the ecosystem. Indications such as similar effects observed in humans that can be demonstrated on teleosts. This may elicit some suspicions that SSRI exposure may function in the same way in humans and teleosts. To be able to tie the effects of SSRI exposure in teleosts relevant biomarkers are required. Therefore further research into this is required since other substances, heavy metals and pollutants exist in the environment that may cause alterations in teleosts.

Other indicators demonstrating the effects that may be caused by SSRI exposure are the facts that the substances have been found in tissue in fish and in that of samples from water from the WWTPs. The tests would need to be based on field testing scenarios, implementing a mixture of substances as well as tests where several species in larger pools that are mixed and exposed to the similar substance to see how the whole community is affected. More research would also be needed to find relevant biomarkers and to be able to tie effects to a certain type of exposure.

A reasonable conclusion to be drawn is that SSRI do have the potential to cause effects on interspecificity in aquatic environments. Since both physiological and behavioural alterations have been observed in teleost exposed to SSRI. Physiological traits altered can be developmental, deformities, disruptions in physiological functions. Behavioural alterations can result in decreased feeding, aggression, boldness, shelter seeking, nest building, shyness, and reproductive behaviours. Many of which are important for a species function and survival in a food web of aquatic environments (Sebire et al. 2015; Schultz et al. 2011; Valenti et al. 2012; Stanley et al. 2007; Hedgespeth, Nilsson and Berglund 2014; Brooks et al. 2003). Alterations can make a population and individual's easier prey for predators (Hedgespeth, Nilsson and Berglund 2016). Since SSRI have been demonstrated to elicit potential effects on teleosts a reasonable conclusion are to be made that teleosts native to the Baltic Sea may also be affected by SSRI exposure. Since SSRIs have been identified in aquatic systems in the Baltic Sea catchment area (Vieno et al. 2017) it may be reasonable to suspect is has consequences for its teleost species.

Although the additive, non-additive and neutralizing effect between pharmaceuticals, suspended particles and solids that could interact in a natural aquatic environment (Altamura, Moro and Percudani 1994; Arnold et al. 2014; Backhouse 2014) must be taken into evaluation when risk analysis are made. Although the potential to bioaccumulate and bioconcentrate of SSRI it have been observed that over time to reach such concentration in teleost fish that it may exhibit physiological or behavioural effects (Stanley et al. 2007; Corcoran, Winter and Tyler 2010; Foran et al. 2004). This may come to pass even though the concentrations observed in the aquatic environment is below standardized levels of detection of what's considered harmful in tests

(Woldegiorgis et al. 2007). Over time the concentrations can reach such levels in tissue that in this way can be harmful and hazardous to teleosts (Corcoran, Winter and Tyler 2010).

The effects of SSRI exposure as discussed can range from altered physiological traits, behavioural patterns and a species function in the aquatic food web and ecosystem (Sebire et al. 2015; Stanley et al. 2007; Lepage et al. 2005; Kohlert et al. 2012; Werner and Peacor 2003). Since it has been demonstrated that SSRI in aquatic environments effect teleost behaviours and physiology which possibly could affect the whole aquatic ecosystem. In a complex ecological community organisms of different sizes in a food web, why a local extinction can have devastating consequences. Trait alterations in a species have been demonstrated by a series of studies to be interacting with food web and community properties, as it can be explained that if a species changes a behavioural influence, another species population can change and be effected as a result. This could have consequences for other species in the food web and in turn can affect the entire ecosystem. If an keystone species for the ecosystem is strongly affected, it would have a faster and more distinct effect within the food web (Werner and Peacor 2003). Ultimately, ecosystems can be affected, as the food webs, especially in the Baltic Sea, are sensitive and alterations of a species behaviour and function in a local environment will cause population density increases or decreases. It can have cascade and ripple effects up and down in the food web (Johannesson and André 2006; Werner and Peacor 2003).

When one or more species are affected, it can be concluded that the balance of a food web can be compromised and this can lead to serious consequences. Since a food web is interconnected, all species depend on each other in a network of interactions, interdependent relationships of predator-prey circumstances. Should a keystone species become locally extinct this can affect the entire food web (Werner and Peacor 2003; Arnold et al. 2014).

Chronic toxicity is reached in long-term scenarios when teleosts are exposed to SSRI substances over a lifetime perspective, from fry to adult individuals. This may result in severe consequences and effects than what may be observed and can be achieved in acute toxicity tests in clean water tanks. Potential biomarkers may be of assistance in connecting effects to specific sources of exposure (Corcoran, Winter and Tyler 2010; Stanley et al. 2007; Handy, Galloway and Depledge 2003; Arnold et al. 2014; Brodin et al. 2014), such as SSRIs. Furthermore this may be concluded to have the potential to effect aquatic ecosystems when species and food webs are altered. Moreover it is important to keep in mind that other substances and compounds than SSRI may elicit similar effects within the aquatic environment and communities as well. In addition it is a reasonable conclusion that the relative level of concentration for SSRIs in the aquatic environment is of lower significance since teleostes bioaccumulate the substances throughout its life time and in this sense concentrations found in its tissue may reach harmful levels over time.

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