Fate of pharmaceuticals in the environment
-A review-

Maria Kalyva

Student
Theoretical Geoecology in Earth Sciences 15 ECTS
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Supervisor: Jonathan Klaminder

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Abstract

The occurrence of pharmaceuticals in environment originating from human consumption has received increased scientific attention during the last decades due to concerns regarding their combined environmental effects in aquatic and terrestrial environments, in flora and biota and by extent in human health. In this review, I summarized the existing knowledge on the entire life cycle of pharmaceutical substances, from their exposure (sources) and fate to their effects on the natural environment. Since the negative effects of several drugs along with the environmental damage they entail are now known, it can be suggested that pharmaceutical companies make greener pharmaceutical products to reduce these effects to the terrestrial and aquatic environment. The present review could provide suggestions to improve the pharmaceutical environmental management globally, such as methodologies for monitoring systems, that need to be put in place for consistent data collection. Another area of research that is important is the release of pharmaceutical compounds in manufacturing plants as well as from landfill effluent. Finally, one more area with need for further research is green chemistry which could reduce or even eliminate the potential hazards of pharmaceutical compounds that enter the environment, irrespective to the source of entry.

Key words: fate, pharmaceuticals, effects, terrestrial - aquatic environment, solution.

1. Introduction

1.1 Pharmaceuticals and their history

It is well known that the use of pharmaceuticals dates thousands of years back, to ancient Hindu, Chinese and Mediterranean civilizations and there are records of ancient physicians, such as the Greek Galen, that used various drugs in their practice (Encyclopedia Britannica, 2008). These early medicinal substances that were back then available to relieve from pain, were natural extracts and were found as herbs, plants, roots, vines and fungi (Jones, 2011). After the Dark and Middle ages, during the 16th century, Western medicine started recovering and pharmaceutical practice began developing again (Encyclopedia Britannica, 2008). It was only after World War II, however, that, along with synthetic organic chemistry's progression, chemical drug discoveries and usage developed rapidly and continued growing thereafter (Pharmaceutical Sciences University of California Irvine, 2011). The newfound knowledge that synthetic chemicals had the potential to kill or immobilize parasites, bacteria and microbes selectively, led to massive research and industrialization of chemical pharmaceuticals that continues to the present (Chemical & Engineering News, 2005).

1.2 Occurrence in the environment

Following this acute development, we now know with confidence that aquatic environments nowadays receive continuously mixtures of drugs on a global scale (Boxall et al., 2012). Their most popular uses, among others, include human medicine, where they serve as tools for the treatment or prevention of various diseases, veterinary drugs or husbandry growth promoters with applications on many different aspects of agriculture (Halling-Sørensen et al., 1998). Pharmaceuticals include more than 4000 molecules with different physico-chemical and biological properties and distinct modes of biochemical action (Beausse, 2005; Boxall et al., 2012).

Recent evidence indicates that the use and consumption of pharmaceuticals per capita in the European Union has doubled or nearly tripled on a time span of only 14 years (2000-2014) and suggests an inference of an even bigger absolute consumption amount due to continuous global population increase (OECD, 2014). This critical piece of information highlights the demand of further investigation of these substances and their possible effects on the environment. The numerous potential effects of pharmaceutical substances along with their sources in the environment have been widely studied during the past years. After administration, some drugs are metabolized, while others remain intact until they are excreted. Pharmaceuticals and their metabolites can either enter the aquatic systems via excretion or disposal wastewater. Due to their high polarity and low volatility, most pharmaceuticals are most likely to be transported to the water column (Breton and Boxall, 2003).

The main trail pharmaceuticals follow to surface waters is through domestic, industrial or hospital effluents and via effluents from waste water treatment plants (WWTP), where pharmaceuticals are incompletely removed. In fact, research suggests that up to 90% of the drug residue can be found in the effluent leaving the treatment plant (Cooper, Siewicki and Phillips, 2008). The combined excretion of active pharmaceutical ingredients can take place via urine and feces, which is the direct route through which drugs enter the environment. The indirect route is considered to be the disposal of unused or leftover drugs by flushing into sewers (Daughton, 2009).

Pollution from the production of pharmaceuticals, occurring by industrial waste disposal, was not considered a major factor of the release of drugs into the environment until recently. Contemporary research shows, however, that certain production sites can cause environmental pollution at levels way above than previously thought (Fick, 2009). Other ways pharmaceuticals can reach the aquatic environment include, for example, via runoff water from the agricultural sector, through the disposal of sewage sludge, where pharmaceuticals are used for veterinary purposes (Kümmerer, 2009), or leaching to ground waters after rainfall

(Topp et al., 2008). Today pharmaceuticals can be found everywhere, including sediment, medical sewage, WWTP, surface water, groundwater, drinking water, in the arctic environment (Fatta-Kassinos, 2010) and in biota.

The occurrence of pharmaceuticals in the environment has been widely studied, continuously providing increasing numbers of reports from drugs detected in potable water, river water, sea water or waste water. Garrison and colleagues (1976), were the first to report traces of pharmaceuticals in treated wastewater. A major limitation on the study of pharmaceutical substances so far though, has been the fact that they cannot be easily detected and qualitatively analyzed (Boxall et al., 2012). Among other reasons, the most important ones include the lack of critical methodological approaches and the fact that most studies have focused on investigating the processes and mechanisms behind the degradation of pharmaceuticals in laboratory settings. Since the latter largely lacks the complexity occurring in natural environments (Klaminder et al., 2014), one of the goals of contemporary studies is to simulate degradation in natural environments. The fate of pharmaceuticals and their eventual effects on ecosystems are, therefore, until recently not well known (Arnold et al., 2014). Figure 1 shows the sources of pharmaceutical substances explained above and their fate that will be described in the next subchapter.

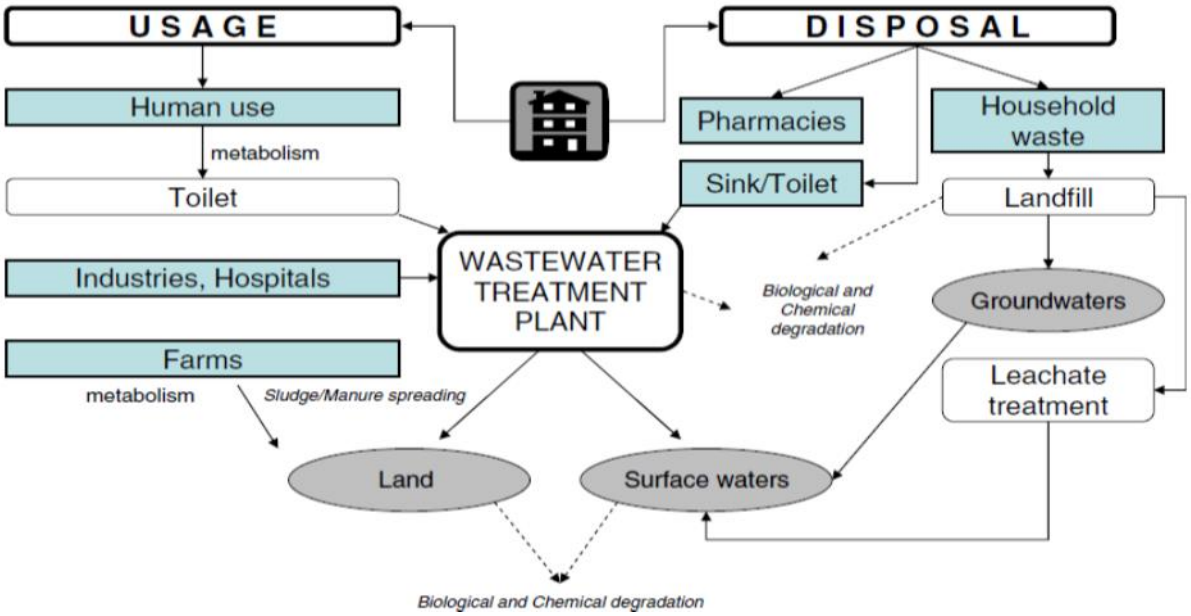

Fig. 1 Sources and fate of pharmaceutical substances into the environment (Nikolaou et al., 2007).

1.3 Fate of pharmaceutical substances in the environment

Current research highlights the need for further study of the fate and the removal mechanisms of pharmaceutical substances along with the released amounts of them. The dissipation of pharmaceuticals in the aquatic environment is controlled by different processes. The main processes include aerobic and anaerobic bio-degradation and abiotic transformation such as degradation of UV-light, hydrolysis and sediment sorption. Depending on the properties of the specific compound of the drug and the characteristics of the surrounding environment, we can determine which of the above processes is most effective.

According to recent reports, aerobic and anaerobic bio-degradation are the most important processes for removal of pharmaceuticals from the dissolved phase. The percentage of drugs removed from the system rises along with hydraulic retention time and the age of the sludge. Diclofenac, for instance, was found in previous research to have been bio-degraded only when the sludge retention time was at least 8 days. Abiotic transformation of drugs in

surface water or wastewater can take place via hydrolysis, photolysis or sedimentation. As drug compounds are often resistant to hydrolysis, this reaction can be characterized negligible for most human drugs. Direct and indirect photolysis, on the contrary, is a primary route of abiotic transformation of pharmaceuticals in surface waters. Direct photolysis is the result of direct absorption of sunlight, while indirect photolysis includes natural photosensitizers (Nikolaou et al., 2007).

According to Halling- Sørensen et al., (1998), the drugs can be divided in three principal possible fates: i) the substance is mineralized to carbon dioxide and water, e.g. aspirin (Richardson and Bowron, 1985) ii) the substance is lipophilic and not readily degradable so part of this will be retained in the sludge iii) the substance is metabolized to a more hydrophilic form of the parent lipophilic one, but still persistent and therefore it will pass the WWTP and end up in the receiving waters (waste water treatment effluents often discharge to rivers) and may further affect the aquatic organisms if the metabolites are biologically active. Substances with the potential to be retained in the sludge, will, given that the sludge is dispersed on fields, be able to affect the micro-organisms and beneficials. The medical substances used for animals in stables as growth promoters will most likely end up in manure.

Drugs used in human medicine are designed to have biological effects and to be bio-available. Only recently, however, has there been increasing concern over the trace amounts of pharmaceuticals found in the environment and their possible consequences (Daughton and Ternes, 1999). Although pharmaceuticals have long been released to the environment, recent concern derives partly from the fact that new analytical methods are now able of detecting pharmaceuticals at levels found in the environment (Erickson, 2002). During the past decades, more than 100 different drugs have been detected in the aquatic environment at concentrations from the nanogram (ng) to the μg/l range (Kummerer, 2001). Furthermore, as pharmaceuticals are continuously released into the environment, organisms are expected to be exposed to many of these substances for their entire lifespan. Therefore, it is possible that pharmaceuticals may impact non-target organisms in the aquatic and terrestrial environment (Boxall, 2004).

Some pharmaceuticals are recently being associated with adverse developmental effects in aquatic organisms and with negative impacts on human health. Although several drugs are unlikely to constitute a risk, as they are found in low concentrations combined with low toxicity, e.g. iopromide (Steger-Hartmann et al., 2002), other pharmaceuticals such as natural and synthetic sex hormones are now known to pose considerable risks for the aquatic environment (Nash et al., 2004). In addition, pharmaceutical substances have been found in groundwater (López-Serna et al., 2013), often explained due to direct or indirect impact of waste water (Sacher et al., 2001). Pharmaceuticals have also been found in biota from algae to fish in various concentrations and all over the world (Grabicova et al., 2015; Liu et al., 2015).

Potential bioaccumulation and persistence of released pharmaceuticals is also widely debated. Moreover, pharmaceuticals released into the environment as mixtures also raise concerns, as the combined environmental effects of pharmaceuticals have been for long unknown (Stackelberg et al., 2004). In addition to potential ecological risks, human health might also be at risk through long-term consumption of drinking water containing trace levels of pharmaceuticals. Although the compounds of drugs in drinking water are at doses far below the ones used in therapy, drinking water standards have not yet been established for most pharmaceuticals. The figure below (fig.2) illustrates in general the exposure, the fate and the effects of pharmaceutical substances.

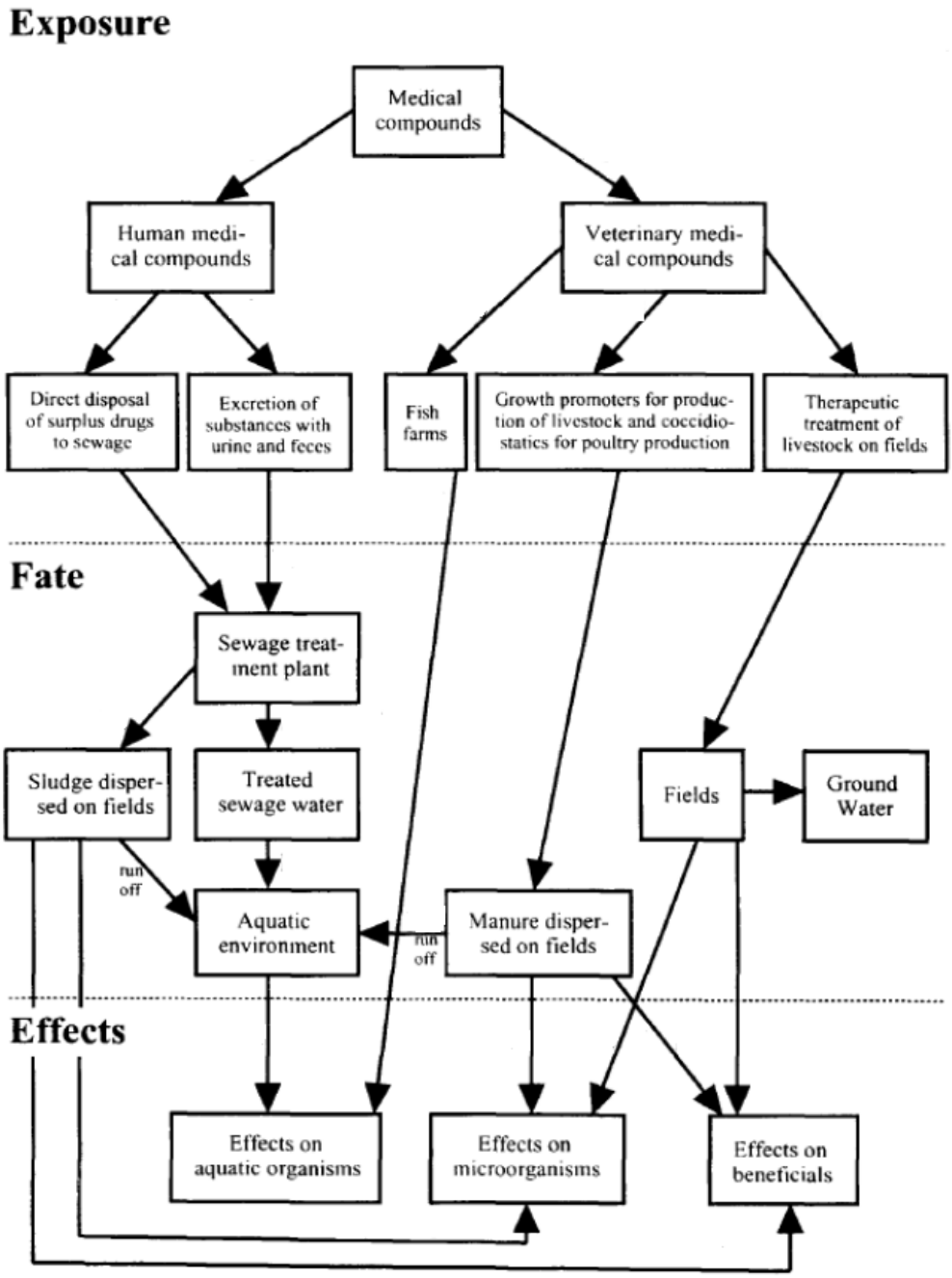

Fig.2 Routes of both veterinary and human pharmaceutical substances in the environment (Halling- Sørensenet al., 1998).

1.4 Aim

Large volumes of data have been generated during the past decade on the fate and occurrence of pharmaceuticals in the environment; therefore, it seems like the time has come to concentrate all this knowledge to a review and attempt to detect the risk and the damage that pharmaceuticals can cause to aquatic and terrestrial environment to biota and even to humans. Since the negative effects of some drugs are now known, it can be suggested that pharmaceutical companies make greener pharmaceutical products to reduce these effects to the terrestrial and aquatic environment. Results of this study could provide information on levels, sources and potential risks of pharmaceutical substances, for protecting water and terrestrial resources and improve the environmental management globally.

2. Methods

The literature search was conducted with the use of research tools at Google Scholar, Web of Science and the University Library Database. Key words included 'fate of pharmaceuticals', 'aquatic and terrestrial environment'. Other methods of literature search were also employed aiming on an as-exhaustive-as-possible search, such as search in reviews bibliographies etc. Prior to the present review, I submitted my master thesis about the fate of pharmaceuticals in aquatic environments in Northern Sweden. Cited articles from that paper were also used without further research. No further limitations were applied.

3. Results and Discussion

3.1 Occurrence and Exposure to the Environment

Medical substances have been measured in the effluent of medical care units, sewage and the effluent of sewage treatment plants, in surface water, groundwater, and in drinking water (Heberer, 2002). Seasonal variations have been studied in sewage and reclaimed wastewater, as well as in finished water (Alexy et al., 2006). Pharmaceuticals have also been detected in the effluent from landfill sites. Meanwhile, there is evidence of the occurrence of approximately 160 different drugs in STP effluent, surface water and ground water. Surprisingly enough, pharmaceutical substances were also detected in the arctic remote environment (Kallenborn et al., 2008).

The findings of the concentrations of pharmaceuticals have been confirmed for different countries and different environmental compartments (Kummerer, 2008b). Castiglioni et al. (2008) showed in their survey that only recently psycho-active and illicit drugs such as amphetamine, cocaine and its metabolite benzoylecgonine, morphine, methadone and its main metabolite and amphetamines have been detected in surface water and wastewater. Daily and seasonal variability was examined and revealed fluctuations in the concentrations of nicotine, paraxanthine, amphetamine, cocaine, and ecstasy during the week, where the estimations of consumption were made using the total concentrations found in wastewater (Castiglioni et al., 2008).

The knowledge about pharmaceuticals in sewage sludge and biosolids is necessary for the proper understanding of fate, and for risk assessment, although as Jones - Lepp and Stevens (2007) suggested, little is known about the occurrence, fate or activity of metabolites. It is possible that their effects on environmental organisms may be milder than those of the parent component, however, in the case of pro-drugs the situation is probably different, as it may also be for the metabolites of several other pharmaceuticals such as norfluoxetin (Nalecz-Jawecki, 2007).

3.2 Potential quantities

Samuelsen et al. (1992) suggested that 70 -80 % of drugs administered in fish farms end up in the environment, and drug concentrations with antibacterial activity are found in the sediment underneath fish farms. Because a major part of medical substances applied in human treatment may be metabolized by the liver, a substantial amount will be exposed as metabolites. The total usage of some veterinary pharmaceuticals applied in Sweden (antibiotics and antiparasitics) 1988 to 1993 and in Norway (antibiotics) is discussed in Bjornerot et al. (1996). During the period studied, the total usage of antibacterial substances remained stable in Sweden at approximately 35 tons of active substance annually. The use of antibiotics for growth-promoting purposes was prohibited in Sweden in 1986 and became available by veterinary prescription only. In 1996 the total amount of coccidiostatics was around 10 tons annually and other antiparasitic drugs up to 7.7 tons annually. A study

conducted in 1985 by Richardson and Bowdon on the exposure of human drugs to the River Lee, in England, showed that approximately 170 pharmaceutical chemicals were found to be used in amounts exceeding 1 ton annually. Gibson and Skett (1986) in their survey explain that most medical substances are metabolized to phase I or phase II metabolites before being excreted from the body with the urine and may be exposed to the environment. Phase I reactions usually consist of oxidation, reduction or hydrolysis, and the products are often more reactive and sometimes more toxic than the parent drug. Phase ll reactions involve conjugation, which normally results in inactive compounds. In 2001, estimates for the use of antibacterials alone totaled 92,500 to 196,400 kg in aquaculture and 8.5 to 11.2 million kg in agriculture in the United States (Boxall, 2004).

3.3 Sources

Hospitals

As expected, pharmaceuticals are present in hospital wastewater (Schuster et al., 2008). The concentrations of pharmaceuticals in hospital wastewater are higher than in municipal sewage. However, the total substance flow is much lower because of the much lower share of effluent from hospitals in municipal effluent in developed countries. Kummerer and Helmers (2000) observed that the dilution of hospital wastewater by municipal wastewater is by much more than a factor of 100.

Private households

Expired medicines or their leftovers are usually disposed of households via the sewerage. In accordance with EU legislation, the discarding of unused drugs via household waste has been permitted since 1994. As it is reported by Ronnefahrt (2005), approximately 1/3 of the total volume of pharmaceuticals sold in Germany and about 25% of that sold in Austria (Sattelberger, 1999) is disposed with household waste or down the drain. A conducted poll has found that 17.7% of those surveyed get rid of excess and outdated pills by pouring them into the toilet, and, about 20% do the same with liquid pharmaceuticals (Gotz and Keil, 2007).

Moreover, a survey carried out in the UK investigating the household disposal of unused and expired pharmaceuticals interviewed members of 400 households, predominantly from south-eastern England, and was the basis for a conceptual model aiming to assess the pathways of human pharmaceuticals into the environment. The model demonstrated that the disposal of unused pharmaceuticals, either by household waste or via the sewerage, may be a prominent route that requires greater attention (Bound and Voulvoulis, 2005). More than half of the patients asked in a study conducted in the US reported storing unused and expired medications in their homes, and more than half had flushed them down a toilet. Only 22.9% reported returning medication to a pharmacy for disposal. Less than 20% had ever been given advice about medication disposal by a health care provider (Seehusen and Edwards, 2006).

In a study performed in Kuwait (Abahussain et al., 2006) almost half of the respondents (45.4%) obtained medicines by prescription more than three times a year and almost all had unwanted drugs in their homes. The reasons for possessing unused medication were mostly due to a change of prescribed medication by the doctor (48.9%), or self-discontinuation (25.8%). Their most common method of disposal was throwing unwanted medicines in the trash (76.5%) or flush them down the drain (11.2%). The results of this study suggest that patient education on the proper disposal of unused and expired medications in all countries is critical. In some countries take-back systems are already in place (Niquille and Bugnon, 2008).

Landfills

The occurrence and fate of pharmaceuticals in landfills has been largely neglected. Once discarded in municipal solid waste, pharmaceuticals within a landfill may undergo degradation, adsorption, or enter the leachate and eventually exit the landfill (Musson et al., 2009). This survey provides information pertinent to the life cycle analysis of pharmaceutical

compounds and when coupled with landfill leachate data enables the assessment of the effectiveness of landfill disposal of pharmaceutical compounds. Moreover, if disposed along with household waste, compounds end up on landfill sites where they can enter the landfill effluent (Metzger, 2004). Thus, if there is no collection of the effluent, this may be a source for contamination of surface water or groundwater.

Holm et al. (1995) found distributions of organic compounds originating from waste from the pharmaceutical industry in the down gradient of a landfill. The authors reported findings of e.g. different sulfonamides (concentrations up to 5 mg/1) and propylphenazone (concentrations up to 4 mg/1). These medical substances have been used for human treatment during the period between 1940's and 1970's. As a common practice during that period, waste from pharmaceutical industries were disposed of at landfills with no leachate collection systems. The chemicals may have entered the surrounding aquifers as a part of the leachates (Holm et al. 1995).

3.4 Fate in the environment

In general, sorption of acidic pharmaceuticals to sludge is suggested to not be very important for the elimination of pharmaceuticals from wastewater and surface water. Therefore, levels of pharmaceuticals in digested sludge and sediments are suggested to be relatively low, as was demonstrated in several monitoring studies (Urase and Kikuta, 2005). However, basic pharmaceuticals can adsorb to sludge to a significant extent, as has been shown, for example, for fluoroquinolone antibiotics (Golet et al., 2002).

Degradation in sludge does not seem significant. As a consequence, EE2 (estrogens) occur in digested sludge, where concentrations of 17 ng/g were reported (Temes et al., 2002). In case a pharmaceutical is occurring mainly in the dissolved phase, biodegradation is suggested to be the most important elimination process in wastewater treatment. It can occur either in aerobic (and anaerobic) zones in activated sludge treatment, or anaerobically in sewage sludge digestion. In general, biological decomposition of micro-pollutants including pharmaceuticals increases with increase in hydraulic retention time and with age of the sludge in the activated sludge treatment. For example, diclofenac was shown to be significantly biodegraded only when the sludge retention time was at least 8 days (Kreuzinger et al., 2004).

In contrast, data from Metcalfe et al. (2003a, b) indicate that the neutral drug carbamazepine, which is hardly biodegradable, is only poorly eliminated (normally less than 10%), independent from hydraulic retention times. Pharmaceuticals are often excreted mainly as non-conjugated and conjugated polar metabolites. Conjugates can, however, be cleaved in sewage treatment plants (STP), resulting in the release of active parent compound as shown for estradiol (Ternes et al., 1999), and the steroid hormone in the contraceptive pill, 17-ethinylestradiol (D'Ascenzo et al., 2003).

The removal rates are variable, even for the same pharmaceutical between different treatment plants. Total elimination of 94–100% of ibuprofen, naproxen, ketoprofen and diclofenac was found in the U.S.A. (Thomas and Foster, 2004). X-ray contrast media (diatrizoate, iopamidol, iopromide, iomeprol), on the other hand, were not significantly eliminated (Ternes and Hirsch, 2000). Also, the anticancer drug tamoxifen (antiestrogen) was not reduced (Roberts and Thomas, 2005). This variation in elimination rates can be explained by the fact that pharmaceuticals form a heterogeneous group consisting of compounds with diverse chemical properties.

For other pharmaceuticals (sulfamethoxazole, ofloxacin and propranolol) laboratory experiments indicate direct and indirect photolysis as an important removal process (Andreozzi et al., 2003b). Carbamazepine and clofibric acid have been shown to undergo slow photodegradation in salt- and organic-free water with estimated half-lives in the range of 100 days at latitudes of 50◦N in winter (Andreozzi et al., 2003b). The efficiency of photodegradation depends, besides substance properties, on the strength of the solar irradiation, and therefore on latitude and season.

The disappearance of a substance does not necessarily indicate biological or photochemical degradation. An important pathway for elimination is sorption of pharmaceuticals, which depends on the extent of neutral and ionic species present and the characteristics of the target particles. Sorption may have an impact on the spread and (bio)availability of pharmaceuticals in the environment (particle bound transport), and their removal during wastewater treatment. Laboratory studies detected the sorption behavior of carbamazepine, diclofenac and ibuprofen in sandy sediments and showed that sorption coefficients were generally quite low (Scheytt et al., 2005). For instance, some antibiotics, e.g. tetracyclines, are known to have a tendency to bind to soil particles or to form complexes with ions that are present (ter Laak et al., 2006a, b). The sorption of antibiotics is especially affected by the amount and nature of free and suspended particles in the water phase, soil organic matter and soil (Thiele-Bruhn, 2003).

3.5 Transport

The transport processes of medical substances in the environment are not adequately covered in the literature. The mobility of avermectin, an antiparacetic agent, is described by Gruber et al. (1990). From pesticide research, it is well known that after agricultural treatment, pesticide may move below the ground in both the saturated and unsaturated zones and, depending of the water mobility, end up as parent compound or metabolites in the aquatic environment (Kreuger 1992). It is therefore, anticipated that antibiotics may have the same fate if manure containing antibiotics is spread on fields just before a rain. Several antibiotics have the same physico-chemical properties as the pesticides known to be able to run-off to surface waters (Kreuger 1992).

3.6 Pollution in aquatic environments

Surface, Ground and Drinking water

Only a few references can be found in the literature concerning findings of metabolites originating from medical substances in ground water. A landfill in Florida which received wastes from the Jackson Naval Air Station in 1968 and 1969 including wastes from the naval base hospital, has contaminated a nearby shallow ground water (Eckel et al. 1993). The authors reported the presence and persistence of drugs in the 21 years old anaerobic ground water plume.

Contamination of tap water by clofibric acid (metabolite of a blood lipid regulator in human medical care) was investigated by Stan et al., (1994). This paper showed that samples taken from different districts of Berlin, all containing clofibric acid in concentrations between 10 and 165 ng/I. Clofibric acid was additionally detected in all surface water samples from the Berlin area and was also found in samples of surface waters taken from several rivers in other areas of Germany.

Fick's et al. (2009) study clearly shows that pharmaceutical production severely contaminates surface, ground, and drinking water in Sweden. In this study the contamination of the lakes with milligrams of drugs per liter was 100,000 to 1 million times higher than the reported levels of fluoroquinolones in surface water in the United States and China contaminated by sewage effluents (Koplin et al., 2002, Xiao et al., 2008). The analysis of the well water indicates that the analyzed drugs can contaminate groundwater over large areas, which constitutes a direct route for human exposure. High levels of antibiotics in the influent means an active selection for resistant bacteria. In addition, approximately 20% of human feces, inevitably containing pathogens, are added daily to maintain biological activity. Fick et al. (2009) show that very large volumes of surface and groundwater are contaminated by fluoroquinolones at levels high enough (5–10 mg/L) to promote horizontal transfer of resistance genes (Beaber et al., 2004). The use of contaminated groundwater as a drinking-water source could therefore act as a direct route for resistant bacteria to humans.

It can be assumed that microbial degradation will be slower in surface water than in the sewage system due to its lower bacterial density and lower diversity. Bacteria that are resistant to antibiotics are present in surface water. A correlation between resistant bacteria in rivers and urban water input has been found, as have antibiotic resistance genes (Watkinson et al., 2007). Antimicrobial resistance has also been found in marine bacteria (Neela et al., 2007) and bacteria living in estuaries or coastal waters polluted with sewage water (Kummerer, 2004; Kimiran-Erdem et al., 2007). Even in remote places such as the Arctic Sea, E. coli isolates originating from Arctic birds carry antimicrobial drug resistance. These results show that resistance genes can even be found in a region where no selection pressure exists (Sjolund et al., 2008).

Some pharmaceuticals are known to pass through the floor of rivers and lakes and mix with groundwater (Reddersen et al., 2002; Heberer, 2002], and Massmann et al. recently showed that pharmaceuticals can persist in aquatic environments for decades (Massmann et al., 2008). As exposure to sunlight is considered the most important factor by which fluoroquinolones are degraded in nature (Boreen et al., 2003), it is likely that fluoroquinolones are relatively stable once they reach the groundwater.

Antibiotics are rarely found in ground water and, when they are detected, they usually only occur at concentrations far below the l g /L range. Leaching from fields fertilized with animal slurry or passing through sediments into the ground water might be a source of antibiotics in ground water (Sapkota et al., 2007). However, the volume load of antibacterial agents in ground water in rural areas with high concentrations of livestock has proven to be small.

Direct exposure to pharmaceuticals at levels normally found in drinking water (up to 100 ng/L) is generally not considered to pose human health risks (Johnson et al., 2008). However, the present study shows that drinking water in areas with high levels of industrial waste may be contaminated to considerably higher levels. Although the estimated daily exposure would still be far below normal therapeutic doses for all analyzed drugs, the risk in such areas, could be particularly regarding exposure during pregnancy and childhood (Collier, 2007). In figure 3 Weber shows the global situation regarding the drugs found in surface ground and drinking water.

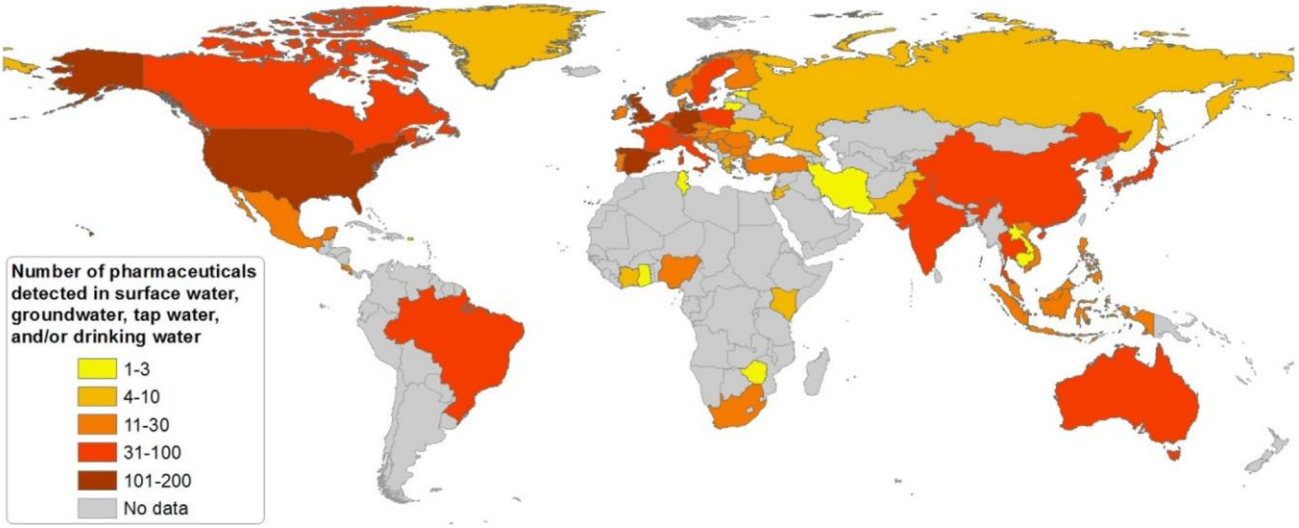

Fig 3. Survey on the number of pharmaceutical substances detected in surface waters, groundwater, or tap/drinking water (Weber et al., 2015).

River pollution

Domestic sewage pollution is caused by various effluent sources in urban river water (Kiguchi et al., 2016). Watts et al. (1983) reported the presence of several antibiotics (erythromycin, sulphamethoxazole, tetracyclines) and theophylline, in river water samples. Aheme (1984) and Aheme et al. (1985) have used techniques for the detection of the presence of methotrexate, progesterone, norethisterone and ethinyloestradiol in various river and potable water samples. The latter study reported that detection limits between 5 and 10 ng/L were achieved.

Futhermore, in a study by Paiga et al. (2016), in Portugal, the occurrence of 33 pharmaceuticals and metabolites was evaluated along the Lis river and in the influents and effluents of two wastewater treatment plants (WWTPs) located along the river. Non-steroidal anti-inflammatory drugs/analgesics were the therapeutic group with a high contribution to the total mass load of pharmaceuticals entering the Lis river, followed by psychiatric drugs and antibiotics. No seasonal variation was observed for the detected concentrations of pharmaceuticals (Paiga et al., 2016).

Ocean pollution

Nowadays, ocean acidification and increasing discharges of pharmaceutical contaminants into aquatic systems are among key and/or emerging drivers of environmental change affecting marine ecosystems. A growing body of evidence demonstrates that ocean acidification can have direct and indirect impacts on marine organisms although combined effects with other stressors, namely with pharmaceuticals, have received very little attention to date (Freitas et al., 2016). The findings of Freitas et al. (2016) add to the growing body of evidence that ocean acidification will act to increase the toxicity of some pharmaceutical substances to marine organisms, which has clear implications for coastal benthic ecosystems suffering chronic pollution. Furthermore, Lee and Arnold (1983) examined a deep-water dumpsite, receiving 30 to 280 million liters of pharmaceutical waste annually, during the period from 1972 to 1983 in the United States, at 74 km north of Areciho, Puerto Rico, and covered an area of about 500 Km^2. Unfortunately, no information was available on the content or occurrence of the wastes.

3.7 Pollution in terrestrial environments

Soil – Sediment pollution

Pharmaceuticals can enter the soil environment when animal slurries and sewage sludge are applied to land as fertilizers or during irrigation with contaminated water. These pharmaceuticals may then be taken up by soil organisms possibly resulting in toxic effects and/or exposure of organisms higher up the food chain. A survey by Carter et al. (2016) investigated the influence of soil properties on the uptake and depuration of pharmaceuticals (carbamazepine, diclofenac, fluoxetine and orlistat) in the earthworm Eisenia fetida, and their results demonstrate that a combination of soil properties and pharmaceutical physico-chemical properties are important in terms of predicting pharmaceutical uptake in terrestrial systems and that pharmaceuticals can modify soil and internal earthworm chemistry which may hold wider implications for risk assessment.

Chlortetraeyclines were found in soil amended with poultry manure (Warman and Thomas 1981). It was demonstrated that drug metabolites excreted by medicated livestock are decomposed by bacterial action in the liquid manure and reconverted into the active drugs. Due to the application of manure to agricultural soils, multiple drug resistance developed in livestock micro flora and even in the intestinal flora of untreated pigs. Thus, multiple-resistant 366 strains found their way into the food chain (Berger et al., 1986). Shore et al. (1988) presented findings of testosterone and estrogen, used as growth promoters, in chicken manure. A paper published by Gool van (1993) estimates that if the total amount of growth promoters used in the Netherlands were spread over the 2 million hectares of Dutch arable land, a yearly

average of 130 mg antibiotic and antibiotic metabolites per m ^{2} of arable land would be found. If this amount were located in the top ten cm of the field, a concentration of 0.87 mg/kg of soil should be expected.

Several investigations describe findings of antibiotics in sediment cores from medication in fish farms (Kerry et al., 1995). For example, Oxytretracycline, an antibiotic agent, was found, by Jacobseb and Berglind (1988) in concentrations varying between 0.1 and 4.9 mg / kg dry matter.

High loads of antibiotics in sediments at concentrations enough to inhibit the growth of bacteria have been reported for aquaculture (Kummerer, 2004). Resistant bacteria may be present in sediments because of the application of antibiotics in fish farming or because of selection through the antibiotics present in the sediments. The substances used in fish farming can enter sediments directly from water without undergoing any kind of purification process. Some investigations have demonstrated the presence and persistence of antibiotics applied extensively in fish farming in sediments beneath fish farms (Kummerer, 2004). Fluoroquinolones, sulphonamides and tetracyclines are strongly adsorbed, therefore, they can readily accumulate in sediments. In the fish farming sector (aquaculture, marine-culture, etc.), the widespread use of antibiotics for treating bacterial diseases has been associated with the development of antibiotic resistance (Serrano, 2005).

A study performed by Hektoen et al. (1995) shows a comparison of the persistence of oxytetracycline, oxolinic acid, flumequine, sarafloxacin, florfenicol, sulfadiazine and trimethroprim in marine sediments. These substances were found to be very persistent in the sediment. In the deeper layer of the sediment the initial concentrations of these compounds were present after 180 days and a calculated half-life of more than 300 days was estimated. The residues in the top layer of the sediment depurated more rapidly. The removal of these substances from the sediment was, according to the authors, most probably due to leaching and redistribution rather than degradation.

Sewage sludge

In a study by Chen et al (2013), a total of 45 dewatered sewage sludge samples were collected from China and analyzed for 30 commonly consumed pharmaceutical residues. Poor agreement was concluded between the predicted and detected concentrations of the pharmaceuticals, indicating that the occurrence of pharmaceutical residues was affected by various factors such as loading rates, sewage properties and the chemical properties such as the contribution from polar groups. The authors suggest further study of national wide fate and ecotoxicity for the development of control strategies.

Richardson and Bowron (1985) examined several pharmaceutical substances for their biodegradability during sewage treatment. The substances were selected for biodegradation studies on basis of their high quantity in use, their potential for being noxious or based on literature reviews that indicated that the drug had the potential to 'survive' sewage treatment. The methods for testing were those recommended by the Department of Environment, Standing Committee of Analyst (1981) and King (1981). Kiirnmerer et al. (1996) showed that some antinoplastic agent were persistent in sewage sludge.

3.8 Effects - Risks - Impact on Populations

Contemporary studies consider the adverse effects on humans to be negligible, although it is known that aquatic organisms are nowadays most at risk and there is limited research concerning the effects of pharmaceuticals on humans. Studies also indicate that population groups have a similar response to the exposure to the pharmaceuticals, and therefore, there is no difference in consumption for a fetus, baby, child, to the elderly (Kummerer, 2009). Another issue of concern is the possibility that exposing bacteria within our water to antibiotics (parent as well as metabolite compounds) could increase their resistance to the antibiotic effects (Cooper, Siewicki, & Phillips, 2008).

As drugs are designed to have biological effects in small amounts, most pharmaceuticals produced are water soluble and they are not prone to biomagnification (Sherer, 2006). That is, as other compounds build up within the fat of organisms, the effects of the natural food chain cannot reach the larger animals consuming more and the amounts therefore increase rapidly within them.

The most obvious risk associated with the findings in Fick's (2009) study is that the high levels of broad-spectrum antibiotics could induce the development of antibiotic-resistant microorganisms. The increasing occurrence of multiresistant pathogens is a serious global threat to human health and is promoted by the heavy use of antibiotics in human and veterinary medicine. Industrial wastewater containing antibiotics can select for resistant strains of bacteria in the environment (Guardabassi et al., 1998).

Cleuvers (2008) found that toxicity of a mixture of non-steroidal anti-inflammatory drugs against Daphnia was considerably higher even at concentrations in which the single substances showed no or only very slight effects. Remarkably, reproduction was decreased by 100% at concentrations where no effects on survival could be observed, which means that this destructive effect on the Daphnia population would be totally overlooked by an acute test using the same concentrations. Effects occurred even at the lowest treatment level with concentrations that were still 1000–5000 times higher than measured concentrations in the environment.

There is no information about the bioaccumulation potential of pharmaceuticals in biota or food webs with the exception of diclofenac, the most well studied pharmaceutical globally, accumulating in the prey of vultures (Oaks et al., 2004), fluoxetine, sertraline and the SSRI metabolites norfluoxetine and desmethylsertraline detected in fish (Brooks et al., 2005). Diclofenac bioconcentration factors were 10–2700 in the liver of fish and 5–1000 in the kidney, depending on exposure concentrations (Schwaiger et al., 2004).

Indirect effects

Pharmaceuticals in the environment can have implications for certain species in different ways. It has been found that detrimental effects may happen if compounds are transferred within the food web chain. Between 2000 and 2003, high annual adult and sub-adult mortality (5–86%) in the oriental white-backed vulture and the resulting declines in population (34–95%) were associated with renal failure and visceral gout. A direct correlation of residues of the anti-inflammatory drug diclofenac with renal failure was found. Diclofenac residues and renal disease were reproduced experimentally in oriental white-backed vultures by direct oral exposure and through feeding vultures' diclofenac-treated livestock (Oaks et al., 2004). Other findings show that veterinary use of diclofenac is likely to have been the major cause of the rapid vulture population declines across the subcontinent (Taggart et al., 2007).

Another example of indirect effects of antibiotics was reported by Hahn and Schulz (2007). Results of food selection experiments with Gammarus pulex demonstrated clear preferences for leaves conditioned in the absence against those conditioned in the presence of two antibiotics, oxytetracycline and sulfadiazine. Other examples are the intersex of fish that is exposed to estrogen (Jobling et al 2006) and this feminization can severely disturb a fish population (Kidd et al 2007). Pharmaceuticals in the aquatic system can also affect the behavior of fish and this has been proved by Brodin et al (2013), who found that oxazepam (a drug to treat anxiety) altered behavior and feeding rate among European perch even in concentration levels found in natural surface waters.

Toxic Effects

Micro-organisms

Sanyal et al. (1993) said that ibuprofen, which has analgesic, anti-inflammatory and antipyretic properties (Reynolds 1989), and is taken orally to treat mild to moderate pain of rheumatism and other musculoskeletal disorders, draws into attention the potential antimicrobial activity of ibuprofen against certain dermatophyte fungi. The same authors also noted that Staphvlococcus aureus was susceptible to ibuprofen. Growth of Staphvlococcus aureus was suppressed by ibuprofen concentrations greater than 150 mg/L at initial pH 7, while, at pH 6, such concentrations prevented growth. Furthermore, Lee and Bird (1983) found that the calanoid copepods Temora turbinata, if raised in pharmaceutical waste concentrations above 1 ppm, resulted in smaller adult size, reduced egg production and an abnormal growth pattern.

Phytoplankton

Streptomycin prevented growth of six blue-green algae species in an investigation performed by Harrass et al (1985), at concentrations (0.09 to 0.86 mg/1). Chlorella vulgaris, &'enedesmus obliquus and Ulothrix sp. grew in active streptomycin concentrations less than 21 mg/L, while Chlamvdomonas reinhardtii growth was prevented at concentrations of 0.66 mg/L. Algal growth in sub-lethal concentrations of streptomycin was slowed or delayed, and the maximum density attained by several species was decreased.

Plants

Batchelder (1981: 1982) showed that effects of the antibiotics chlortetracycline and oxytetracycline on plants vary from species to species. The most sensitive plant species in the Batchelder's study was pinto beans when they were grown on sandy loam soil. The acute toxicity of furazolidone, which is largely used in medicated fish feed, has been investigated by Macri et al (1988) and the authors found a significant toxicity of the compound on Daphnia Magna, while Artemia salina proved to be the less sensitive. Migliore et al. (1997) showed the toxicity of several agricultural antibiotics to Artemia. Acute toxicity of four antibiotics: aminosidine, bacitracin, erythromycin and lincomycin, all used as feed additive or mass therapy in intensive farming, on Dapnia magna Straus has been reported by Dojmi di Delupis et al. (1992).

Amphipods - Invertebrates

Lee and Arnold (1983) studied the toxic effects of ocean-dumped pharmaceutical wastes on the marine amphipod Amphitoe valida. The toxic effects increased with increasing duration of exposure to waste concentration. Amphipods chronically exposed to waste concentrations above 1% had lower survival rates and reduced fecundity when compared to control groups. The parent amphipods exposed to 3% waste had 100 % mortality after three weeks, while those exposed to less than 2 % waste were able to survive over 2 months. Nicol et al. (1978) have shown that the pharmaceutical wastes disposed of at the Puerto Rico dumpsite were toxic to many invertebrates, thus, toxic levels were about 0.05 - 5% of the waste concentration, depending on species employed in the bioassay. Lagesson et al., 2016 detected the uptake of five pharmaceutical substances in four aquatic invertebrate taxa (damselfly larvae, mayfly larvae, waterlouse, and ramshorn snail, significant differences among drugs in their capacity to bioaccumulate and differences among species in uptake, where clearly detected.

Fish

Only little information is outlined in the literature concerning the effects of medical substances on fish species. The performed ISO laboratory assays with ibuprofen show that the compound is almost non-toxic on bluegill sunfish and sheepshead minnow (Knoll, BASF 1995). The latest study detecting the effects of some pharmaceutical substances is by Lagesson et al.,

(2016) that assess to what extent five pharmaceuticals (diphenhydramine, oxazepam, trimethoprim, diclofenac, and hydroxyzine) are taken up by fish (European perch), by tracing their bioconcentrations over several months in a semi-natural large-scale (pond) system. The results suggest both significant differences among drugs in their capacity to bioaccumulate and differences among species in uptake.

Insects

Macri et al. (1988) showed that furazolidone had a significant toxic effect on the mosquito larvae. Whereas drugs such as piperazine, thiabendazole and levamisole has little or no effect on clung beetle breeding, formulations of coumaphos, dichlorvos and phenothiazine adversely affected their survival and reproduction for at least 4 to 5 days after treatment (Blume et al., 1976). Phenothiazinc was also associated with deleterious changes in the botanical composition of pastures (Southcott, 1980), whereas residues of dichlorvos delayed dung degradation (Lumaret 1986).

In the late 80"s Wall and Strong (1987) discovered that avermectin, an antiparasitic drug for cattle treatment, had an effect on dung degrading insects and delay in degradation of pats from cattle treatment was observed. The environmental aspects and effects of avermectin have all been investigated by Holter (1993) and results show that the duration of effects after treatment of ivermectin on dung degrading organisms is depended on species, temperature, soil composition and type of livestock.

Ecotoxicological effects

Pharmaceuticals are designed to target specific metabolic and molecular pathways in humans and animals, but they often have important side effects as well. Thus far, ecotoxicity testing provided indications of acute effects in vivo in organisms of different trophic levels after short-term exposure, and only rarely after long-term (chronic) exposures. (Fent, 2001). Contemporary literature about ecotoxicological effects of human pharmaceutical deals mainly with the acute toxicity in standardized tests and is generally focused on aquatic organisms. Moreover, effects of drug metabolites have rarely been investigated. Photo-transformation products of naproxen, for instance, showed higher toxicities than the parent compound, while genotoxicity was not found (Isidori et al., 2005).

Fick et al. (2009) suggested that it is also evident that the levels of fluoroquinolones measured will have ecotoxicological effects, particularly on microbial ecosystems. As bacteria play important roles in the cycling of energy and nutrients, effects on microbial ecology may indirectly have unanticipated consequences for other parts of the ecosystems. The growth of frog tadpoles, for example, exposed to the effluent diluted 1:500 was strongly impaired (Carlsson et al., 2009).

Acute effects

Acute toxicity data of pharmaceuticals were studied by Webb (2001), who provided a list of about 100 human pharmaceuticals from different sources. By comparing different trophic levels, the researcher suggested that algae were more sensitive to the listed pharmaceuticals than Daphnia magna, and fish were even less sensitive. In the attempt to compare the different classes of pharmaceuticals in terms of acute toxicity, the author noted that the most toxic classes were antidepressants, antibacterials and antipsychotics (Webb, 2001).

The U.S. Geological Survey took the first national look at pharmaceuticals and other compounds within the water. This study took place in 1999-2000, and found organic wastewater contaminants, in 80% of the streams they examined (Kolpin, et al., 2002). In another survey, fluoxetine (anti-depressant, Prozac) and its metabolite were tested for their effects on bivalves. This study was conducted due to the rates found within streams and sewage effluent, 0.012 μg/L and 0.099 μg/L respectively 116 (Fong & Molnar, 2008), so concerning fluoxetine and its metabolite norfluoxetine, reproductive behaviors of bivalves are affected. At

certain concentrations, reproduction is induced within the bivalve, which can result in the wrong reproductive periods and therefore effects upon the larvae and juveniles as food and conditions can reduce survival rates. Another study looked at intersex, the presence of both female and male reproductive characteristics, within bass fish and these reproductive effects have previously been linked to endocrine active compounds which include some forms of pharmaceuticals (Hinck, et al., 2009).

3.9 Solutions to the Problem

The first method to begin with in order to resolve the problem is the generation and improvement of waste programs both through businesses (including hospitals and providers) as well as the general public. Restrictions on hospitals and other providers have been established by the Resources Conservation and Recovery Act of 1976 (RCRA) that gives the Environmental Protection Agency (EPA) the right to control management and disposal of hazardous wastes (United States Environmental Protection Agency, 2008). After these federal restrictions, increasing state regulations strive to tighten the practices of these businesses.

Unfortunately, there is limited education provided to individuals regarding the proper disposal of their medications and other chemicals. In order to resolve this problem, educational materials could be displayed within drug stores and more information could be provided by pharmacists and doctors. Moreover, the current federal guidelines should include the disposal of drugs via sewage, unless indicated on the label or on the FDA website. Furthermore, if drugs cannot be disposed this way, they should be disposed of within community take-back programs or mixed with cat litter or coffee grounds in a sealable bag or container before placed in the trash (Office of National Drug Control Policy, 2009).

Another method to reduce the amount of pharmaceuticals in the environment is through changes within water/sewage treatment systems. They are currently not equipped to deal with the treatment of such chemical compounds. In addition, this would help mitigate the effects from livestock excrement and agriculture runoff. Therefore, there will still be amounts of pharmaceuticals entering the sewage and water systems if they are not specifically addressed within treatment methods (Office of National Drug Control Policy, 2009).

4. Conclusion

Overall, the research for pharmaceuticals in the environment is growing and nowadays we can say that is a well-studied and debated topic, but there remain many areas in need. Firstly, methodologies for monitoring systems need to be put in place for consistent data collection. Another area of research that is important is the release of pharmaceutical compounds in manufacturing plants as well as from landfill effluent. Finally, one more area for further research is the potential for green chemistry which would reduce or even eliminate the hazards of pharmaceutical compounds that enter the environment, despite of the source of entry. According to the principles of green chemistry (Anastas and Warner, 1998), the functionality of a chemical should not only include the properties of a chemical necessary for its application, but also fast and easy degradability after its use. Introducing green chemistry in terms of economy, however, may prove to be a challenging endeavor. The situation looks worse than 20 years ago, and now we understand better the potential eco-toxicity of many pharmaceuticals and mixtures of medicines that enter the environment during their production, consumption and disposal. We need to move from environmental risk assessment of a few drugs to far more comprehensive environmental stewardship of pharmaceuticals across their full life cycles, including manufacture. Lastly, there is also a need to improve the waste management and we need robust information to guide the public and policymakers.

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Dept. of Ecology and Environmental Science (EMG)
S-901 87 Umeå, Sweden
Telephone +46 90 786 50 00
Text telephone +46 90 786 59 00
www.umu.se