

Pharmaceuticals in the Environment: An Overview & Brief Insight into Northeast Ohio

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Background & Extent of the Problem

There has been an increasing concern of pharmaceuticals (as well as other organic contaminants) within water sources. These compounds have been found within medical sewage, sewage treatment plants, surface water, ground water, drinking water, and the arctic environment¹. Therefore, this issue is not isolated to a certain area and will continue to grow and move through the water system unless actions are taken. In a pivotal study of the field, the U.S. Geological Survey conducted the first national look at pharmaceuticals and other compounds within the water. This study took place in 1999-2000, and found organic wastewater contaminants (of the 95 contaminants surveyed for) in 80% of the streams they examined². A review of the literature found that the interest has grown in the last 15-18 years within studies, analysis, and publications³.

There are a plentitude of manners in which pharmaceutical and other organic compounds can enter the water system. When an individual takes medication, it is not all metabolized and used within the body. Instead, if you follow the source of human excretion, in the form of urine, 30 to 90% of a given drug dose is excreted⁴. Some other methods include “direct runoff of on-ground fecal material from pets and livestock, prophylactic treatment of terrestrial and aquaculture livestock, release from industrial production of pharmaceuticals, use of sewage sludge as fertilizer, and use of treated wastewater for irrigation”⁵. An in-depth visual depiction of the origin and fate of pharmaceuticals and personal care products (PCPs) in the environment which is outside the scope of this report can be seen in appendix 1. Although treatment plants have various methods to treat waste and chemicals within the sewage and water, they are not designed to eliminate these pharmaceuticals and other organic compounds. In fact, with their current methodologies, up to 90% of the drug residue can be found in the effluent leaving the treatment plant⁶.

This is a growing concern, because water is a vital resource for all of human life, and the fresh water supply is limited. Moreover, as research in this field is relatively new, there are many unknowns associated with the long-term exposure of bacteria, organisms, and humans to these drugs and their metabolite forms within the environment. 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 alone⁷. Consider also oral contraception which is used by more than 10 million females in the United States and excreted into the water system. In addition, there is a growth in prescription drugs. From the time period 1988-1994, only 39.1% used a prescription in the last month, while in the time period 2003-2006 this statistic increased to 46.9%⁸. The issue of pharmaceuticals in the environment has also been closely studied within Northeast Ohio. A study of Tinkers Creek and other tributaries that lead to the Cuyahoga River discovered pharmaceutical compounds both present in upstream and downstream effluent of

¹ (Kummerer, 2009)

² (Kolpin, et al., 2002)

³ (Kummerer, 2009)

⁴ (Cooper, Siewicki, & Phillips, 2008)

⁵ (Cooper, Siewicki, & Phillips, 2008)

⁶ (Cooper, Siewicki, & Phillips, 2008)

⁷ (Boxall, 2004)

⁸ (National Center for Health Statistics, 2010)

wastewater treatment plants as well as in soil sediment (as can be seen in appendix 2)⁹. Pharmaceuticals and other organic compounds are currently within our water systems and will continue to increase in concentration unless active steps are taken.

Toxicology

In addition to the numerous methods by which pharmaceutical compounds and other organic compounds enter the environment, there are also a variety of forms the pharmaceuticals take on within the environment. First, there are active pharmaceutical ingredients (APIs) which are complex molecules and are considered to be “small molecules”¹⁰. They are classified into groups in different ways, such as according to their purpose and biologic activity, their mode of action, and chemical structure. Regardless of their classification structure, each group still has extreme differences within the chemicals, as even small changes such as in the chemical structure means entirely different reactions within the environment¹¹. This is not the only concern as in the last few years research has broadened from just the APIs into also studying the reactions of the parent compound. The parent compounds have demonstrated changes within their structure and this can result in changes in their effects upon the environment based on their metabolism as well as other transformations that may occur (for example through excretion from animals or chemical reactions from treatment facilities)¹². Additionally, there are many possible combinations of compounds that can arise due to what is within the water. In a 2009 published review of the literature, Kummerer states that it is imperative to separate the nomenclature of these various compounds as studies occur as their individuality will lead to different effects and risks to the environment – essentially changes in their toxicology within the system. Therefore, it is not possible to come up with standard toxicology across the pharmaceutical compounds that enter the environment, and further research is needed.

Environmental Health Risk Assessment

The U.S. Food and Drug Administration (FDA) mandates that environmental risk assessments be performed on any human and veterinarian drug before reaching the market¹³. These assessments look at the effects on aquatic and terrestrial organisms, but the validity of the current research has been questioned. The tests conducted are standard and typically involve an acute exposure that looks for mortality¹⁴. Also, the tests on aquatic organisms do not study the compounds within the sediments. Overall, these studies require a larger concentration than what currently exists naturally. However, not as much is known regarding chronic exposure as well as the combination of compounds within nature.

Pharmaceuticals within the environment, although currently at an amount considered to be negligible, gives rise to multiple concerns. These compounds are specifically designed to create a specific response within those it is administered to (humans, animals). Therefore, the amounts within the environment and the limited amount of information regarding the breakdown and effects are areas in need of development. Some concerns that have been voiced include “abnormal physiological processes and reproductive impairment, increased incidences of cancer,

⁹ (Tertuliani, Alvarez, Furlong, Meyer, Zaugg, & Koltun, 2008)

¹⁰ (Kummerer, 2009)

¹¹ (Kummerer, 2009)

¹² (Kummerer, 2009)

¹³ (Boxall, 2004)

¹⁴ (Boxall, 2004)

development of antibiotic-resistant bacteria, and the potential increased toxicity of chemical mixtures”¹⁵.

Studies have been conducted on the environmental health risks regarding specific compounds and their effects, specifically on aquatic organisms. In one study, 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 respectively¹⁶. This serotonin reuptake inhibitor is excreted by humans at 20-30% in its original form and the rest within metabolites. 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 lessen survival rates. Currently, the concentrations needed for this effect are not seen within streams tested, little is known regarding chronic accumulation effects or the rate of increase within compounds in the environment¹⁷. Another study looked at intersex, the presence of both female and male reproductive characteristics, within bass fish. These reproductive effects have previously been linked to endocrine active compounds which include some forms of pharmaceuticals¹⁸. Like many studies within this field, further information is needed in order to determine the direct causation of these changes. In addition to some examples provided here, Boxall, in a review of studies regarding aquatic and terrestrial organisms, indicates the reported effects of a selected substance on the organism, which can be found in appendix 3¹⁹.

Most risk assessment is based upon the reactions of a single compound. As earlier stated, due to metabolites, transformation, and other reactions, pharmaceuticals do not exist within only their pure states and the effects of both their possible combinations and accumulation within organisms needs to be accounted for²⁰. Therefore, approaches to the environmental risk assessments of these pharmaceutical compounds need to be explored.

Impact on Populations

Most at risk currently are aquatic organisms as described in the previous section. There is limited research concerning the effects of pharmaceuticals on humans. However, current studies regard the adverse effects on humans to be negligible. Currently, detection of pharmaceutical compounds is in the nanograms per liter range which is considered two orders of magnitude less than an amount needed for a human effect²¹. For consumption of 2 liters for 70 years, the amount over the life-span still remains under dosages utilized in prescriptions²². Although this indicates overall consumption effects, it also does not take into consideration the differences between short-term high concentrations (used in prescriptions) against this chronic long-term small dosage exposure (from concentrations in drinking water and the environment). Moreover, it considers each population group to have a similar response, so there is no difference in consumption for a fetus, baby, child, to the elderly²³.

¹⁵ (Kolpin, et al., 2002)

¹⁶ (Fong & Molnar, 2008)

¹⁷ (Fong & Molnar, 2008)

¹⁸ (Hinck, Blazer, Schmitt, Papoulias, & Tillitt, 2009)

¹⁹ (Boxall, 2004)

²⁰ (Kummerer, 2009)

²¹ (Sherer, 2006)

²² (Kummerer, 2009)

²³ (Kummerer, 2009)

Another item of concern is the potential that exposing bacteria within our water to antibiotics (parent as well as metabolite compounds) could increase their resistance to the antibiotic effects²⁴. This would then necessitate an immediate response by our current medical practices in order to respond to bacteria for both humans as well as animals. However, this is currently speculation, as there is a lack of direct evidence that antibiotics with bacteria can create resistance. There have been cases beginning to show antibiotic resistant genes and microbes that have been found in water containing antibiotics, but further scientific understanding is needed²⁵.

The difficulty to remove these compounds in treatment systems furthers the need for research regarding the impact on aquatic and terrestrial organisms, as well as humans and especially the more vulnerable populations. Current treatment options multiple methods to reduce the concentration of the compounds. In addition, in some processes, byproducts are formed which can be more persistent than the parent compound²⁶. In order to understand more about the impact on populations, specifically the vulnerable populations, research must be conducted to include the byproducts made through the treatment of these compounds.

As drugs are designed to have biologic effects in small amounts, their potency in trace amounts may have effects²⁷. As most pharmaceuticals produced are water soluble, they are not prone to biomagnification²⁸. That is, as other compounds build up within the fat of organisms, the effects of the natural food chain leave the larger animals consuming more and the amounts therefore increasing rapidly within them.

In order to fully understand the impacts of these pharmaceuticals on the population, different approaches to monitoring and testing must be taken. As these compounds breakdown and combine, their specific toxicity to the environments they are in (both aquatic as well as the sediment) need to be analyzed. Moreover, the human downstream effects such as reaching the drinking water and long-term exposures are also crucial.

Resolve Problem

The first method to begin resolving the problem is the generation and improvement of waste programs both through businesses (including hospitals and providers) as well as with 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 wastes²⁹. After these federal restrictions, increasing state regulations strive to tighten the practices of these businesses. For example, in Illinois, the “Safe Pharmaceutical Disposal Act” came into effect on January 1, 2010. This legislation prohibits the disposal of unused medications into public wastewater by healthcare institutions. Further, policies and practices regarding the disposal must be in place for hospitals, nursing homes, residential health care facilities, home health care agencies, hospice programs, mental health providers, and developmental disabilities providers³⁰. As regulations begin to tighten on the disposal of hazardous wastes, organizations should either create internal mechanisms to monitor and meet the standards, or outsource these capabilities to

²⁴ (Cooper, Siewicki, & Phillips, 2008)

²⁵ (Cooper, Siewicki, & Phillips, 2008)

²⁶ (Boxall, 2004)

²⁷ (Sherer, 2006)

²⁸ (Sherer, 2006)

²⁹ (United States Environmental Protection Agency, 2008)

³⁰ (Falbe, Swill, January, & Villasenor-Rodriguez, 2009)

organizations such as Stericycle that are equipped for proper segregation, transportation, and treatment of healthcare waste.

Currently, 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 pharmacies as well as from those providers writing the prescriptions. Although many prescriptions are intended to be taken until they are finished, in many instances leftover compounds are disposed of in improper methods including flushing into the water treatment system or in trash refuse. The current federal guidelines include that drugs not be flushed unless indicated on the label or on the FDA website. Further, if drugs cannot be flushed, they should be disposed of at community take-back programs and if not available, mixed with cat litter or coffee grounds in a sealable bag or container before placed in the trash³¹. In a survey conducted in the United States, more than half of patients kept expired and unused medications and more than half had flushed them down a toilet³². Moreover, only 22.9% reported returning them to a pharmacy and less than 20% ever had education regarding medication disposal³³. These statistics demonstrate the large gap in education needs that can be rapidly improved from providers and pharmacies to their individual patients as well as on a larger scale. This method is the first priority due to ability of any education and training to be able to increase the 20% whom have had education previously regarding medication disposal. The form of education is also economical, as it requires little time and monetary investments by all parties involved. For instance, pharmacies can post posters regarding proper disposal as well as inform people on pick-up of how to take care of the drugs. A paper could be placed within the prescription bag with the information detailing proper disposal for this type of drug. Policy guidelines could mandate that pharmaceuticals be accompanied by information regarding its proper disposal method. Other benefits of employing this method are that individuals have a stake in the proper disposal, as this can directly reduce drug abuse (for instance family members finding/improperly utilizing the drugs), and drug related accidents.

In furthering the proper disposal of pharmaceuticals, drop-off/take-back programs could be increased. The organization and collection of these pharmaceuticals and controlled substances has a low economic footprint, requiring volunteers as well as uniformed officers and collection bins. The city of Bath (near Akron) in Ohio was recently in the news for their “Going Green and Clean” campaign to collect unused medications³⁴. The drugs are being collected for both the safety of teens as well as the environment. This also assists the community in decreasing the 20% of teens that report having abused prescription drugs³⁵. The medications will be incinerated and disposed of properly after collection is completed. The state of Illinois mandated on August 10, 2009 that the Illinois EPA work with Illinois Department of Public Health to have a program for people to drop off unused pharmaceuticals³⁶.

Another method to reduce 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. The regulations regarding sewage treatment plants include testing for substances, but drugs are not included³⁷. When pharmaceuticals (parent compounds only) were

³¹ (Office of National Drug Control Policy, 2009)

³² (Kummerer, 2009)

³³ (Kummerer, 2009)

³⁴ (Dennee, 2010)

³⁵ (Dennee, 2010)

³⁶ (Falbe, Swill, January, & Villasenor-Rodriguez, 2009)

³⁷ (Sherer, 2006)

tested in a plant in Germany, the current treatment had a variety of effectiveness on 14 drugs – ranging from 7% to 96% removal (only measuring parent compounds and not their metabolites or transformation)³⁸. This is an important aspect, although economically most costly due to the technological changes involved. Even if the public and providers were compliant with the standards for disposal that they are educated on, in human excretion alone, 30 to 90% of a given drug dose is sent into the sewage system³⁹. 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.

A final method to remedy the problem of pharmaceuticals in the environment is to increase green chemistry. The United State Environmental Protection Agency classifies green chemistry as “chemicals and chemical processes designed to reduce or eliminate negative environmental impacts”⁴⁰. By addressing the hazard that causes potential problems from the start can eliminate the downstream effects. Green chemistry involves making safer chemicals and compounds that will not harm the environment as well as reduced waste products and improved efficiency. This would come closer to eliminating the hazard, and is extremely important as contamination cannot be completely avoided due to excretion and other unavoidable methods chemicals enter the water system. Also, green chemistry could target the current methodologies of care for livestock and agriculture products whose runoff also attributes to the contamination. Although green chemistry would be the ideal resolution to this problem by completely removing the hazard, it is also not as feasible or economical as other potential solutions.

Research Needs

Throughout the research presented there have been areas of contention as well as areas with limited information. This relatively new field has continued to grow based upon the number of documents and studies published, but there remain multiple areas that require research. These areas include:

- Methodology and technology for monitoring pharmaceuticals
- Human and organism effects
- Drug toxicology and environmental risk assessment
- Treating wastewater to reduce downstream disposal
- Manufacturing release of pharmaceutical compounds
- Landfill effluent
- Utilizing water testing within sewage for drug action
- Potential for green chemistry

These research areas have been ranked by their practicality in reducing, controlling, and monitoring pharmaceuticals in the environment. First and foremost, methodologies for monitoring systems need to be put in place for consistent data collection. This allows for data to be collected in various water systems and can then drive further research interests. For example, results in a certain pathway or area could lead studies on the organisms present there. Moreover, if a certain effluent or stream has a higher concentration of a certain compound the upstream triggers could be pinpointed and changes be made based upon these findings. There are current monitoring devices and methods that are utilized for both water and soil sediment collection, but

³⁸ (Sherer, 2006)

³⁹ (Cooper, Siewicki, & Phillips, 2008)

⁴⁰ (United States Environmental Protection Agency)

issues arise in the sampling methodologies specifically the rates which chemical samples are taken⁴¹. Furthermore, there are concerns that remain with the position of the longer-term monitors regarding sediment, light, flow of water, and vandalism. These methodologies and technologies are rated as the top priority of research because with technology capabilities they are practical to produce and test. Also, in order for further research to be valid, proper tools must be in place.

Another area of research ranking high on the list based on practicality is researching the effects pharmaceuticals in the environment have upon humans. The key stakeholders in this process (ranging from individuals to legislators, to organizations) are more easily motivated to take action when the effects are directly applicable to themselves. Understanding the effects on humans also can drive funding for further research as well as possible legislation to reduce the contamination. There is little known regarding acute and chronic exposure to these compounds in the environment as well as potential vulnerable populations. Current environmental risk assessment methods have been questioned regarding long-term exposure and the changes within the pharmaceutical compound chemistry. Therefore, new methods need to be researched in order to have a more accurate idea of the effects of these compounds. Linked to understanding the effects on humans and other organisms is learning more about the specific pharmaceutical compound's toxicology – not only on predicted and desired responses and side-effects, but also the breakdown both in and outside of the body. Through understanding the toxicology, the potential effects upon humans as well as other organisms can be better understood. The current research includes the “Pharmaceuticals in the Environment Information for Assessing Risk” (PEIAR) online (<http://www.chbr.noaa.gov/peiar>) which gathers information on many compounds for researchers. At this time, this serves as a useful tool and starts cataloging and assessing toxicity risk within the water from these compounds. However, it dates to 2004 and contains only 349 drugs. As other reports have indicated, the process which these parent compounds break down creates new combinations and changes the toxicity and predicted effects within the waterways. Although the number of drugs continues to grow, this can be made more practical through stricter guidelines before moving to market.

The next area of research that needs to be furthered is options for treating wastewater. Although this proposed solution was not as valuable due to economic implications, it is extremely valuable due to changing the rates in effluent. As referenced previously, appendix 2 outlines the rates of compounds in influent and effluent water in Tinkers Creek⁴². Therefore, identifying new and improved technologies are necessary to reduce the concentration in this water. Current studies look at eliminating pathogens, but pharmaceutical compounds need to also be considered. Although medical waste is currently more regulated and treated differently, some studies indicate it may result in only 3-10% of the pharmaceutical waste accumulation so other steps need to be taken⁴³. Other methods than the currently utilized UV and chlorine need to be further examined including the oxidation process, application of powdered charcoal, and man-made wetlands. However, these technologies all have some major drawbacks for treatment including the unknown compounds and combinations. This is rated higher on practicality, but the costs may demonstrate it is impractical in the future. Presently, there are a variety of studies that differ in their assumptions and recommendations concerning cost⁴⁴.

⁴¹ (USGS, 2004)

⁴² (Tertuliani, Alvarez, Furlong, Meyer, Zaugg, & Koltun, 2008)

⁴³ (Kummerer, 2009)

⁴⁴ (Kummerer, 2009)

Another area of research that is important is the release of pharmaceutical compounds in manufacturing plants as well as from landfill effluent. The amount of pharmaceuticals disposed of in landfills that can lead to the contaminating ground and surface water is unknown due to household waste practices⁴⁵. Manufacturing plants and their release of pharmaceutical compounds is also unknown at this time⁴⁶. With regulations and potential monitoring, the amounts of pharmaceuticals displaced in these forms could be better estimated and controlled. Therefore, further identification of the displacement in these forms is necessary to motivate key stakeholders, and is practical to evoke change.

In addition, an important area of research would be into other ways to utilize the water testing methods and information collected regarding pharmaceuticals in the environment. This is important and practical, as it is necessary to convince stakeholders of the importance of projects for funding. One proposed use of water testing has been for detection and monitoring of illicit drug users in the population. In Italy, cocaine and its main metabolite were found in the River Po and used as an estimate of the number of cocaine users in the area⁴⁷. This was calculated based upon the known number of users whose sewage flows to the Po. Monitoring and trending the predicted drug use based on these concentrations could have implications regarding programs for drug abuse. This is lower on the practicality list due to potential legal ramifications regarding taking action on these measurements, but it could lead to an interesting and useful application of overall pharmaceutical in the environment research.

The final area for research needs is the potential for green chemistry which would reduce to eliminate the hazards of pharmaceutical compounds that enter the environment, despite the source of entry. Continuing funding and incentives to change the chemical make-up of our pharmaceuticals and other products that lead to organic waste can reduce the amount of hazards introduced to the environment greatly. It is the least practical at this time based upon current restriction on pharmaceuticals, as the incentives do not lie on heavy investment to green and sustainable practices.

Overall, the research for pharmaceuticals in the environment is growing, but there remain many areas in need. Through encouraging stakeholder interest, funding can increase and many of these concerns can be studied.

⁴⁵ (Kummerer, 2009)

⁴⁶ (Kummerer, 2009)

⁴⁷ (Zuccato, et al., 2005)

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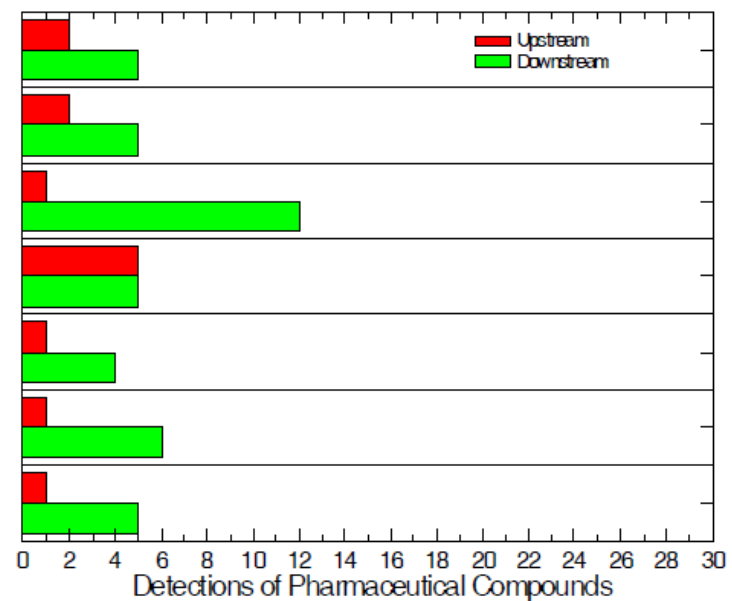
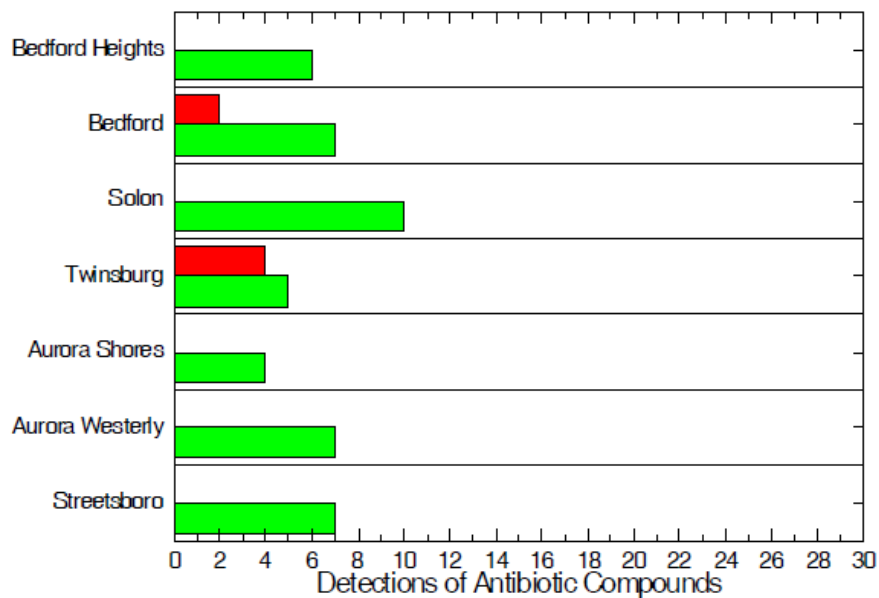
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Appendix 2: Detection of Pharmaceutical Compounds both upstream and downstream of Waste treatment plants



Source: (Tertuliani, Alvarez, Furlong, Meyer, Zaugg, & Koltun, 2008)

Appendix 3: Reported Subtle Effects of Pharmaceutical compounds on aquatic and terrestrial organisms

Table 2 | Reported subtle effects of pharmaceutical compounds on aquatic and terrestrial organisms

Substance(s)	Medicine class	Reported effect	Reference
Fenfluramine	Anorexic	Enhances release of serotonin (5-HT) in crayfish which in turn triggers the release of ovary-simulating hormone resulting in larger oocytes with enhances amounts of vitellin In fiddler crabs, stimulates the production of gonad-stimulating hormone accelerating testicular maturation	Daughton & Ternes, 1999
17a-Ethinylestradiol	Synthetic steroid	Endocrine-disrupting effects on fish, reptiles and invertebrates	Young <i>et al</i> , 2002
Methyltestosterone	Synthetic steroid	Impersex, reduced fecundity, oogenesis, spermatogenesis in snails	Schulte-Oehlmann <i>et al</i> , 2004
Avermectins	Parasiticide	Adults insects: loss of water balance, disruption of feeding and reduced fat accumulation, delayed ovarian development, decreased fecundity and impaired mating Juvenile insects: delayed development, reduced growth rates, development of physical abnormalities, impairment of pupariation or emergence and a loss of developmental symmetry	Floate <i>et al</i> , 2005
Tetracyclines, macrolides and streptomycin	Antibacterials	Antibacterial resistance measured in soil bacteria obtained from sites treated with pig slurry	Sengelov <i>et al</i> , 2003
Cypermethrin	Ectoparasiticide	Impact on dung decomposition	Sommer & Bibby, 2002
Fenbendazole	Parasiticide	Impact on dung decomposition	Sommer & Bibby, 2002
Tylosin	Antibacterial	Impacts on the structure of soil microbial communities	Westergaard <i>et al</i> , 2003
Erythromycin	Antibacterial	Inhibition of growth cyanobacteria and aquatic plants	Pomati <i>et al</i> , 2004
Tetracycline	Antibacterial	Inhibition of growth cyanobacteria and aquatic plants	Pomati <i>et al</i> , 2004
Ibuprofen	Anti-inflammatory	Stimulation of growth of cyanobacteria and inhibition of growth of aquatic plants	Pomati <i>et al</i> , 2004
Fenofibrate	Lipid regulator	Inhibition of basal EROD activity in cultures of rainbow trout hepatocytes	Laville <i>et al</i> , 2004
Carbamazepine	Analgesic	Inhibition of basal EROD activity in cultures of rainbow trout hepatocytes Inhibition of emergence of <i>Chironomus riparius</i>	Laville <i>et al</i> , 2004; Nentwig <i>et al</i> , 2004
Diclofenac	Analgesic	Inhibition of basal EROD activity in cultures of rainbow trout hepatocytes	Laville <i>et al</i> , 2004
Propranolol	Beta blocker	Weak EROD inducer in cultures of rainbow trout hepatocytes	Laville <i>et al</i> , 2004
Sulphamethazole	Antibacterial	Inhibition of basal EROD activity in cultures of rainbow trout hepatocytes	Laville <i>et al</i> , 2004
Clofibrate	Lipid regulator	Inhibition of basal EROD activity in cultures of rainbow trout hepatocytes	Laville <i>et al</i> , 2004
Diazepam	Antianxiety drug	Inhibition in the ability of dissected polyps from the cnidarian <i>Hydra Vulgaris</i> to regenerate a hypostome, tentacles and a foot	Pascoe <i>et al</i> , 2003
Digoxin	Cardiac glycoside	Inhibition in the ability of dissected polyps from the cnidarian <i>Hydra Vulgaris</i> to regenerate a hypostome, tentacles and a foot	Pascoe <i>et al</i> , 2003
Amlodipine	Calcium channel blocker	Inhibition in the ability of dissected polyps from the cnidarian <i>Hydra Vulgaris</i> to regenerate a hypostome, tentacles and a foot	Pascoe <i>et al</i> , 2003

Source: (Boxall, 2004)