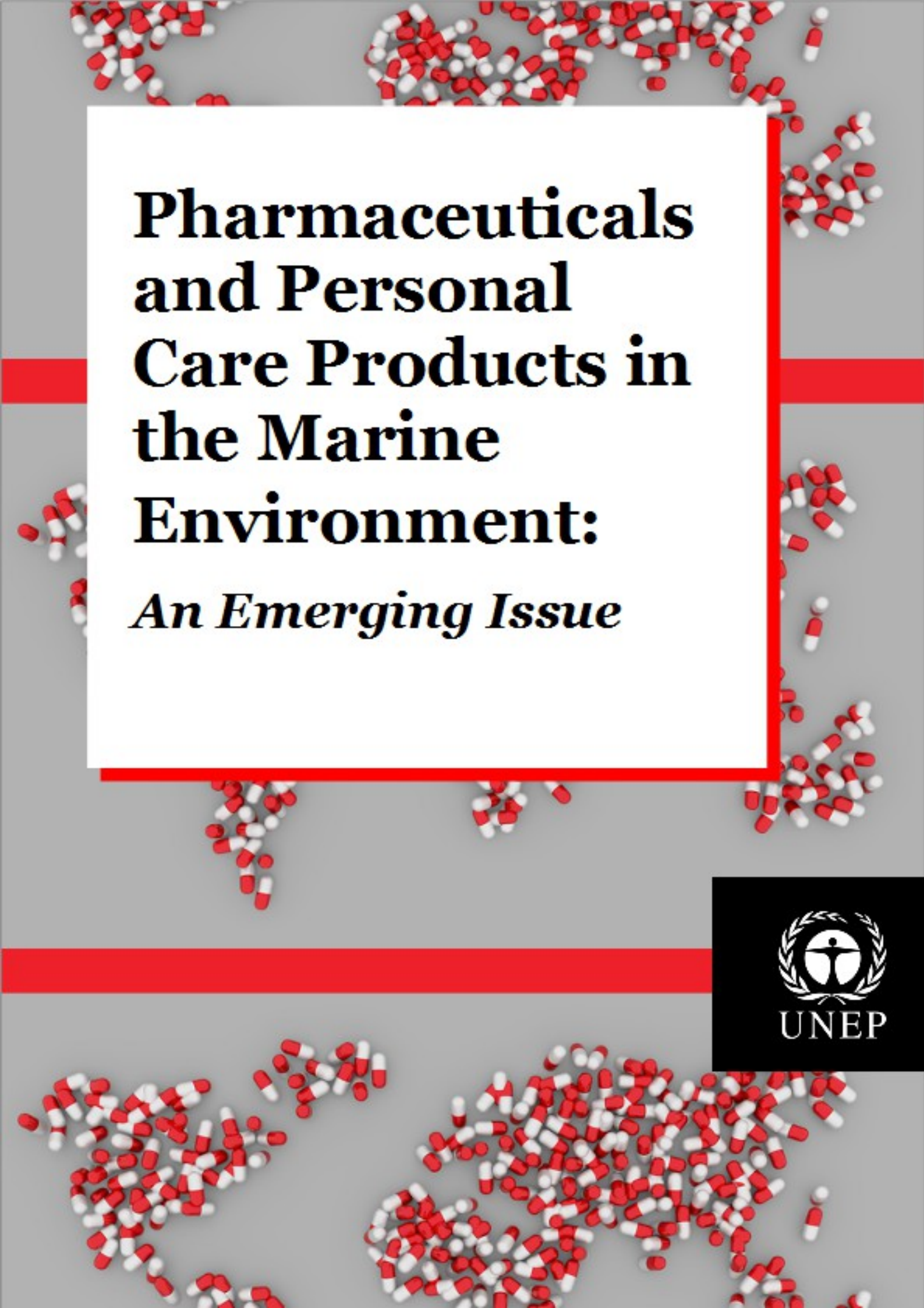

Pharmaceuticals and Personal Care Products in the Marine Environment:

An Emerging Issue

UNEP

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Author: Elizabeth MacAfee

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List of Acronyms

COX	Cyclooxygenase
EDC	Endocrine disrupting compound
EE2	Ethinyl estradiol
EP	Emerging pollutant
KNAPPE	Knowledge and needs assessment of pharmaceutical products in environmental waters
NSAID	Non-steroidal anti-inflammatory drug
PNEC	Predicted no-effect concentration
POP	Persistent organic pollutant
PPCPs	Pharmaceuticals and personal care products
QSAR	Quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals Regulation
SAICM	Strategic approach to international chemicals management
SSRI	Selective serotonin reuptake inhibitor
UN/ECE	United Nations Commission for Eurpoe
WHO	World Health Organization
WWTP	Wastewater treatment plant

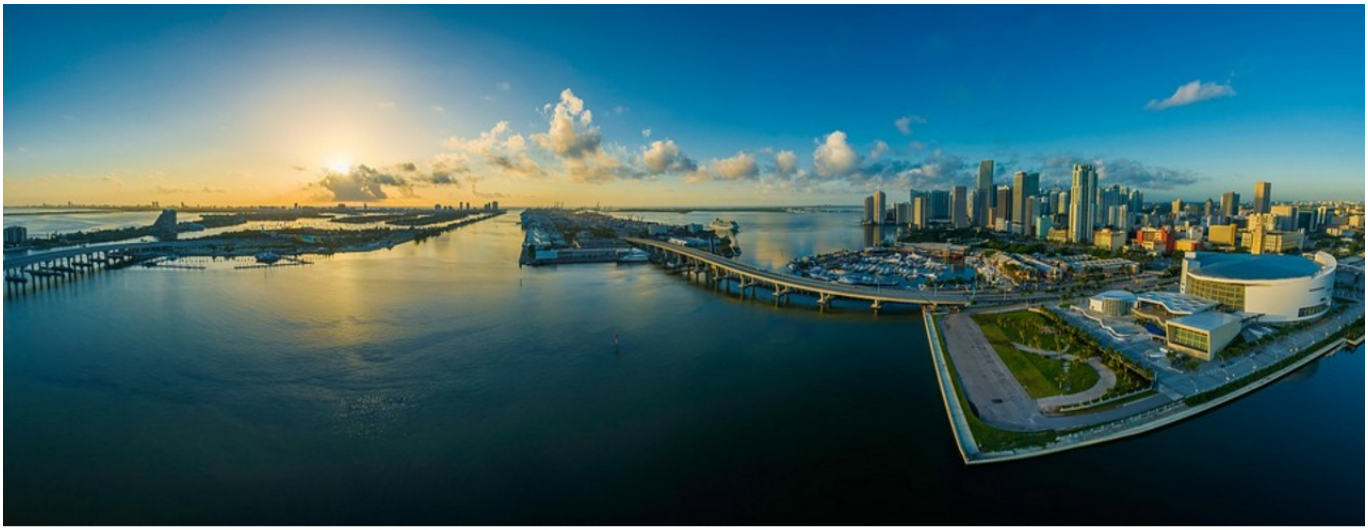
Executive Summary

Chemicals and compounds that have only recently been identified as potential threats to the environment and are not yet widely regulated by national or international law are known as emerging pollutants (EPs). They are classified as 'emerging', not because the contaminants themselves are new, but rather because of the rising level of concern. Awareness of the presence of EPs in drinking water and the aquatic environment is increasing among both the scientific community and the general public as analytical methods for detection of EPs improve and pharmaceutical use continues to grow rapidly (Hendry, 2017).

Pharmaceuticals are intentionally designed to act in ways that make them more likely to be harmful when non-target organisms are exposed to them.

The list of compounds that qualify as EPs is long and getting longer. It includes a variety of compounds: antibiotics, analgesics, anti-inflammatory drugs, psychiatric drugs, steroids and hormones, contraceptives, fragrances, sunscreen agents, insect repellents, microbeads, microplastics, antiseptics, pesticides, herbicides, surfactants and surfactant metabolites, flame retardants, industrial additives and chemicals, plasticizers, and gasoline additives, among others. Many of these substances, particularly pharmaceuticals and personal care products (PPCPs) are different from traditional priority

Source: Pixabay (2017)



Source: Pixabay

pollutants which are acutely toxic, or, in the case of agricultural chemicals, enter the environment in pulsed runoff events after heavy rainfall (Cooper, Siewicki & Phillips, 2008). PPCPs may only exist in the environment in very small concentrations, but they enter it continuously, posing new questions about chronic low-level exposure and mixtures of compounds with additive or unexpected effects.

Municipal wastewater is a primary source of EPs in the aquatic environment. Primary wastewater treatment technology is for the most part not effective in removing EPs, although this varies by location, conditions, and characteristics of each individual EP. Technologies such as ozonation, activated carbon and membrane nanofiltration, and reverse osmosis have the potential to remove some EPs, but more study is needed (Bolong, et al., 2009; Liu et al., 2009).

Pharmaceuticals are intentionally designed to act in ways that make them more likely to be harmful when non-target organisms are exposed to them. For example, some drugs are lipophilic, allowing them to pass through membranes, or they are persistent, which means they are less likely to degrade and become inactive before reaching targets (Halling-Sørensen, et al., 1998). Personal care products, on the other hand, are not typically intended to display significant biochemical activity or treat disease; they are active ingredients or preservatives in cosmetics, toiletries, or fragrances.

Affluent countries account for the vast majority of pharmaceutical consumption, and as such, detection of pharmaceuticals in the aquatic environment has largely been reported in the USA, EU, Japan, and Australia. In the EU, pharmaceutical use is increasing 3-4% by weight each year.

Because of this, the majority of action taken to address PPCPs in the environment has also been in these countries. However, in both international agreements and legislation, EPs and PPCPs are not the primary intended targets of regulations and legislation; they are rather candidates for inclusion under the umbrella of legislation on persistent organic pollutants or toxic substances in drinking-water, groundwater, and wastewater.

In terms of human health and exposure, the WHO (2014) has found that relative to other contaminants in water, such as disease-causing bacteria and pathogens, levels of EPs in drinking water are usually too small to elicit any effect. Concentrations of pharmaceuticals in drinking water have typically been found to be 1000 times lower than the minimum therapeutic dose, usually in the ng L^{-1} to µg L^{-1} range (WHO, 2014). Therefore, according to research carried out over the past decade, impacts on human health from drinking water exposure are extremely unlikely. However, in surface waters and areas in close proximity to point sources of wastewater, concentrations of some EPs have been detected at levels well above predicted no effect concentrations (PNECs). It is important to consider impacts on aquatic ecosystems and also to think about the potential for bioaccumulation of harmful compounds in aquatic organisms that we eat.

Despite legitimate fears of toxicity and cumulative impacts, we must also remember that pharmaceuticals have led to important improvements in health and quality of life, and we should not sacrifice these in order to prevent them getting into the environment. The precautionary principle should guide responses to EPs, but not to the extent that we overreact to substances that may yet prove to be less harmful than expected. By promoting research, monitoring programmes, reductions in waste, and green chemistry it should be possible to prevent and mitigate the negative impacts of pharmaceuticals without compromising on their availability, effectiveness, or affordability, particularly in countries where access to important health services is still limited.

Impacts of Emerging Pollutants

A great challenge when discussing EPs is the large diversity of possible stressor-receptor combinations in non-target organisms which make it very complex to predict what outcomes of exposure will be. Hazardous substances can act at all levels on aquatic biota, and between species, between gender, and between drugs - even within the same class - impacts vary greatly, posing a significant challenge to predictions. It is also difficult to extrapolate from high to low concentration to see what the effects will be because the relationships are often non-linear. Some PPCPs have very high acute aquatic toxicity, while others elicit more subtle effects that are much more difficult to detect (Daughton & Ternes, 1999). Furthermore, some EPs may degrade very quickly, but still have the same level of impact as traditional priority pollutants that are both toxic and persistent because they enter the environment continuously over long periods of time (WHO, 2014).

Many studies have been done on fish, particularly around point sources of pollution; "Because of their ecological niche and similarities in many of their physiological processes compared with mammals, fish are arguably the most likely vertebrate organism to be affected by pharmaceuticals in the aquatic environment" (Corcoran, et al., 2010, p. 288). Less studies are available for other potentially exposed wildlife such as small mammals and birds. Effects have not yet been observed at the population level, and many of the studies discussed below have been done in controlled laboratory conditions with much higher levels of exposure than those that have been observed in nature. Despite these challenges, in this section we will try to discuss generally the impacts of different types of PPCPs as they have been observed in the environment and in laboratory studies.

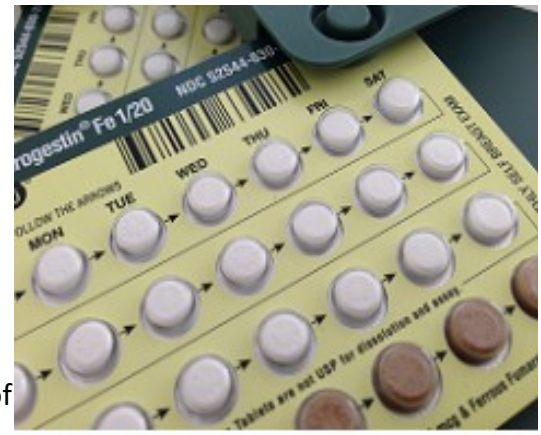
Endocrine Disrupting Compounds (EDCs)

The United States Environmental Protection Agency (EPA) defined an EDC in 1997 as "an exogenous substance that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behavior". EDCs "...disturb the endocrine system by mimicking, blocking or also disrupting function of hormones, affecting the health of humans and animals species" (Bolong, et al., 2009, p. 233).

EDCs include natural and synthetic oestrogens and androgens, phytoestrogens, and industrial compounds like bisphenol A. They have been found in surface waters, sediments, groundwater, and even drinking water, and wastewater treatment plants have been shown to be a major source.

Highly sensitive measurement is needed to detect EDCs because they are active at very low concentrations – in the range of parts per billion or even parts per trillion (Campbell, et al., 2006). Techniques include chemical monitoring such as: liquid chromatography- tandem mass

A household compound with unexpected consequences



Source: Thought Catalogue (https://www.flickr.com/photos/lookcatalog/8602762713)

Ethinyl estradiol, widely known as EE2, is a synthetic estrogen and the active ingredient in most birth control pills. Some estimate that almost 9% of women globally use EE2 to regulate their fertility. Many studies of fish exposure to EE2 have found a broad spectrum of effects, including at environmentally relevant concentrations. These include: "feminisation in fish, including induction of the female yolk precursor vitellogenin (VTG) in males; formation of a female reproductive duct in the testis ; and induction of intersex - the presence of oocytes in the testis" (Corcoran, Winter & Tyler, 2010, p. 291). Lifetime exposure to relatively low concentrations of EE2 has been shown to cause reproductive failure in colonies of zebrafish in laboratories, and "Concentration of 5-6 ng/L of EE2 has been demonstrated to cause population collapse of fathead minnow as a result of feminization of males fish in a Canadian whole lake experiment" (aus der Beek, et al., 2016, p. 832). Levels of EE2 in excess of the predicted no effect concentration (PNEC) of 0.01 ng/L have been reported in 28 countries.

spectrometry, gas chromatography-tandem mass spectrometry, and high performance liquid chromatography (Liu et al., 2009). Bio-assays and effect-based studies may also be useful as endocrine systems are very similar across vertebrate species, and although it may manifest in different ways in different species, disruption is not species dependent (Bergman, et al., 2013). Close to eight hundred chemicals are suspected EDCs, but very few have been studied in detail (Bergman, et al., 2013). Because of these large knowledge gaps, it is possible that impacts have thus far been underestimated.

Effects from EDCs are of particular concern for early development in humans and wildlife because they may be irreversible and not manifest until long after the exposure actually took place. Concerns are rising with evidence of high incidence and an increasing trend of endocrine related effects in wildlife and links between identified EDCs and disease outcomes in laboratory studies. EDCs have been shown to influence male and female reproductive health and impair immune function, and to cause sex-ratio imbalances, thyroid related disorders in children and wildlife, adrenal disorders in children and wildlife, metabolic disorders, and bone disorders. In humans, some studies have suggested that EDCs can lead to a decrease in male sperm count, an increase in testicular, prostate, ovarian, and breast cancers, and reproductive malfunctions (Bolong, et al., 2009). It is also likely that through bioaccumulation and biomagnification their effects will be amplified at the higher end of the food chain (Boxall, 2011).

Analgesics

Analgesics are a class of therapeutic drugs used to relieve pain and inflammation. Some common analgesics are non-steroidal anti-inflammatory drugs (NSAIDs), paracetemol, morphine, and oxycodone. The NSAIDs, including diclofenac, naproxen, ibuprofen, ketoprofen, and indomethacin, inhibit cyclooxygenase (COXs) enzymes that catalyse the production of prostaglandins. Ideally prostaglandins cause inflammation at the site of an injury, but when over-produced they can lead to chronic pain, leading people to manage that pain using NSAIDs (Corcoran, et al., 2010). Most NSAIDs are non-specific, which means they can inhibit

Source: Pierre Dalous via Wikipedia

Unforeseen Danger from a Ubiquitous Compound

Diclofenac is an NSAID used for veterinary purposes, primarily cattle farming, and it is the most frequently detected pharmaceutical globally. It has been found in surface, ground, or drinking water in 50 countries (aus der Beek, et al., 2016). In twelve of those countries, weighted average concentrations exceed PNECs, indicating unacceptable risk to humans and wildlife. It is a frightening example of the potential for PPCPs to have unexpected and very serious consequences on wildlife. In India and Pakistan, mass die-offs of vultures from renal failure and visceral gout associated with exposure to diclofenac in the wild have led to locally dramatic population decline. In India some estimate that the total population of vultures in the country has decreased from forty million to less than one hundred thousand in the last forty years (Nature, 2016; Svanfelt, et al., 2010).

Vultures are exposed to Diclofenac when they consume the carcasses of cattle. Little is known thus far about the *in situ* impacts on marine life from Diclofenac that arrives in aqautic ecosystems via runoff and wastewater effluent, but it has been shown in laboratory experiments to have negative impacts on the health of several aquatic organisms at environmentally relevant concentrations, for example causing damage to inner organs of rainbow trout (aus der Beek, et al., 2016). It is not well removed by most wastewater treatment processes (Svanfelt, et al., 2010), and so it seems likely that a ban on Diclofenac for veterinary use similar to the one in India will be necessary in Europe and other countries that are currently using Diclofenac without restriction. In the EU, Directive 2013/39/EY introduced a watch list on emerging contaminants in groundwater including Diclofenac, 17-beta estradiol and 17-alpha ethinyl estradiol, which is an important positive step, however at this stage there is no comprehensive system in place for monitoring of Diclofenac concentrations or restriction of its use.

unintended production of COXs and cause problems in non-target organisms. In fish, for example, prostaglandins play a role in reproduction by stimulating ovulation. They are also important in cortisol synthesis, which is a key factor in the ability of fish to adapt to seawater (Corcoran, et al., 2010). When fish are exposed to ambient NSAIDs in the environment, both of these processes are at risk of being disrupted. Effects of NSAIDs have been observed at environmentally relevant concentrations, raising concerns that they may already be causing harm to aquatic ecosystems.

Selective serotonin reuptake inhibitors (SSRIs)

In humans, SSRIs are used to treat mood disorders like depression. Serotonin is an important neurotransmitter with influences on behaviour, endocrine activity, and reproduction. SSRIs function by blocking serotonin receptors, preventing the 'reuptake' of serotonin in the brain and making more of it available.

Source: Wikimedia Commons

Antidepressant drugs like fluoxetine (commonly known as Prozac), paroxetine, and setraline, are among the most commonly detected pharmaceuticals in both surface water and wastewater treatment effluents, reflecting their usage volumes in human medicine (Corcoran et al., 2010). These SSRI drugs have been observed at concentrations in the ng L−1 to low µg L−1 range in surface waters and wastewater effluents, and have also been detected in sediment in ng g−1 concentrations. (Corcoran, et al., 2010).

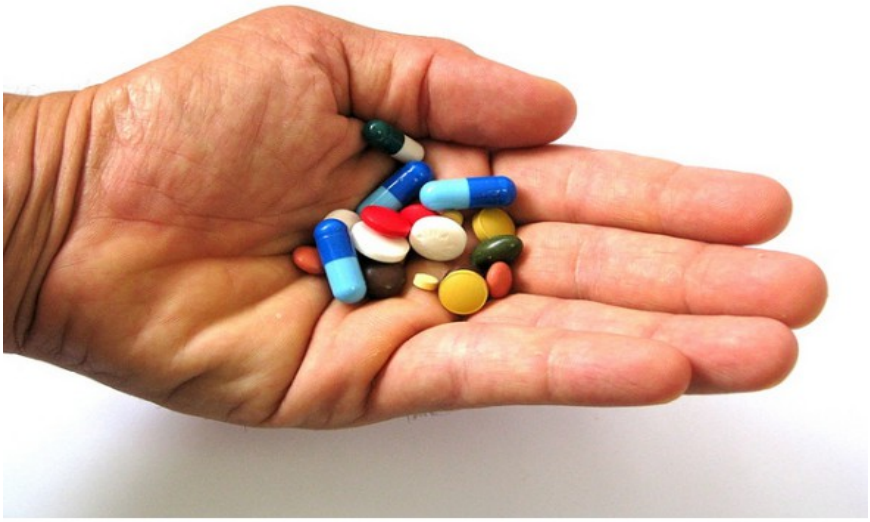
The mode of action of SSRIs can lead to unintended consequences when non-target organisms are exposed. For example, fluoxetine "has been shown to decrease territorial aggressive behaviour in male bluehead wrasse on introduction to an intruder male, in both the laboratory and field, at a concentration of 6 µg g per day over 2 weeks (Perreault et al., 2003; Semsar et al., 2004 in Corcoran, et al., 2010, p. 294)". In other species, fluoxetine has decreased the ability of individuals to capture prey or led to fish maturing during the wrong season due to changes in growth patterns (Corcoran, et al., 2010).

When considered in combination, changes induced by exposure to SSRIs can lead to serious disruptions at the individual and population level because they can induce a constellation of subtle effects across multiple species. These subtle, non-obvious effects have the potential to

accumulate largely unnoticed until they have a significant impact not just on one species but on a whole ecosystem (Daughton & Ternes, 1999). Typically concentrations of SSRIs are quite low in surface water, however they have been found in high concentrations in fish tissues, indicating a potential to bioaccumulate.

Azoles (aromatase inhibitors)

Azoles are a broad spectrum of antifungal drugs that are commonly used in human and veterinary medicine, and have been detected in the environment in small quantities (ng L^{-1} concentrations). Azoles work by inhibiting cell membrane synthesis in fungi, but their inhibition



Source: Victor Casale via Flickr

is non-specific, which means that they have the potential to interfere with steroid biosynthesis and sex hormone balance in non-target species (Corcoran, et al., 2010). Though the quantities of individual azoles detected in the environment has thus far been quite low, they are expected to be present in mixtures. Mixtures of azoles are likely to have similar modes of action, so their effects may be cumulative.

Lipid regulators

There are two major types of lipid regulators. The first are statins, which lower cholesterol, and the second are fibrates, which act on fatty acids and triglycerides. Statins are being prescribed in increasing quantities, but information about their quantity in the environment and ecotoxicology is still largely unavailable. More studies on fibrates exist, but compared to some of the other PPCPs, there is still a dearth of information about their effects. It is, however, known that fibrates are largely secreted unmodified and are very persistent in aquatic environments (Rosal, et al., 2010). They are also not well-removed by traditional wastewater treatment methods. Fibrates have been found at µg L^{-1} concentrations in surface waters and wastewater treatment effluent, and in some cases even at low levels in drinking water (Corcoran et al., 2010). Correlations have been shown between exposure to fibrates and liver cancer in rodents. In fish reproductive effects have been observed including decreased spermatogenisis, reduced sperm count, and limited androgen activity.

Beta-blockers (β- andrenergic receptor antagonists)

Beta-blockers are a class of drugs that are used to reduce blood pressure by blocking the effects of the hormone epinephrine (adrenaline). They are prescribed for patients with angina, heart attacks, arrhythmia, and a host of other conditions. Various beta-blockers have different potency and efficacy towards different receptors. As expected, they also differ in their effects on physiological functions in fish, including cardiovascular regulation, growth, and

metabolism (Corcoran, et al., 2010). For example, propanolol affects heart rate and blood flow through the gills in rainbow trout. In some other fish species, decreased pineal gland production in the presence of beta-blockers can cause changes in activity rhythms and breeding cycles.

Antibiotics

There is an emerging concern that overuse and improper use of antibiotics poses a serious threat to the continued efficacy of antibiotics by encouraging the development of resistant strains of bacteria. Antibiotics released into the aquatic environment through agricultural runoff or domestic and hospital effluent streams may be exacerbating this problem by exposing wild bacteria to antibiotics, thus allowing them to develop resistance in the wild. Resistant strains of bacteria are a very serious threat to our continued ability to use antibiotics for the protection of human and animal health.

Furthermore, the presence of antibiotics in aquatic ecosystems may result in acute toxicity to certain organisms or indirect effects caused by cascades throughout ecosystems. For example, antibiotics may harm 'good' organisms in the environment that are performing denitrification, nitrogen fixation, and organic breakdown.

Others

This list of EPs in PPCPs is by no means comprehensive. Further study is needed on a range of compounds ranging from lifestyle products like caffeine, sweeteners and nicotine, to x-ray contrasting agents, anti-epileptics (ie. Carbemazepine) and barbituates. Illegal drugs, microplastics, and nanomaterials are all entering the environment in increasing quantities and their impacts are still not well understood.

Microbeads, found in personal care products like facial cleansers and toothpastes, are another example. These spherical particles made of polyethylene or polypropylene are difficult for wastewater treatment plants (WWTPs) to remove. Once they are released into the aquatic environment they attract toxins like little sponges, potentially concentrating toxins and causing other problems (Copeland, 2015). In the United States the government found the potential for harm from microbeads to be concerning enough to prompt a ban on microbeads in cosmetics, but they are still being used in many countries around the world.

Pathways to the environment

PPCPs enter the environment in an assortment of ways. The primary sources are drugs excreted or disposed of into the domestic sewer system, leaching from landfills, hospital effluents, and runoff from animal livestock and aquaculture sites (Pal, et al., 2015). Some other locally significant sources include pharmaceutical manufacturers and wastewater used to irrigate field crops (aus der Beek, et al., 2016). The dominant emission pathway in a given location is not often easy to identify, particularly for surface waters.

"Even a seemingly insignificant source such as individual households can add to the level of pharmaceuticals in the water through the addition of expired and unused medicines through sinks and drains..." (Pal, et al., 2015, p. 6063).

Urban wastewater and municipal effluents are a primary source of PPCPs in the environment. Notably, "Even a seemingly insignificant source such as individual households can add to the level of pharmaceuticals in the water through the addition of expired and unused medicines through sinks and drains..." (Pal, et al., 2015, p. 6063). Hospital wastewater often contains extremely high levels of PPCPs

Source: Max Pixel

– ranging from two to one hundred and fifty times the quantity of municipal wastewater – and yet waste from hospitals is frequently discharged into the main urban flows without receiving any advance treatment (Verlicchi, et al., 2010). Typical municipal WWTP are not designed with the goal of removing PPCPs effectively. Hospitals should, in many cases, be treating their effluent for targeted PPCP removal prior to releasing it into combined waste streams.

Source: Jason Turgeon via Flickr

Between fifty-five and eighty percent of the active ingredients in pharmaceuticals are excreted either as unchanged substances, mixtures of metabolites, or conjugated with an inactivating compound (Verlicchi, et al., 2010). Human urine and faeces containing these excreted substances are then carried through municipal sewage systems, and any that are not removed in WWTPs are discharged into local surface or groundwater. Personal care products are often directly released into the environment without passing through any sort of treatment process; lotions and creams wash off in bathing waters and fragrances and musks are sprayed into the air. Discharges to air or land may still end up in surface or ground water through runoff or deposition. From there they may eventually be absorbed or consumed by aquatic life forms or sediments. When disturbed, sediments containing absorbed EPs can release large quantities in short bursts (Hendry, 2017).

Quantities of PPCPs in landfill leachate are also concerning. In January 2010, the Maine Department of Environmental Protection in the United States found hundreds of pounds of the active pharmaceutical ingredients of several over-the-counter and prescription drugs in landfills receiving only domestic waste. This means that significant quantitities of the drugs purchased by or prescribed to patients were being thrown away and ending up in landfills, where they were then able to leach out into surrounding waters. The most common drug detected at all three sampling sites was acetaminophen (117,000 ng/L). Ciproflaxin (269 ng/L) and cocaine (57 ng/L) were also present, as were small quantities of estrone (from hormone replacement therapy), albuterol (an asthma drug) and penicillin (Lubick, 2010).

Another significant source of PPCPs, particularly veterinary drugs and antibiotics, is agricultural runoff. Drugs that are excreted by domesticated animals accumulate on the ground, and during heavy rainfall are washed off to nearby surface waters, or transported downwards through the soil to groundwater. In areas where wastewater and human excreta are reused as fertilizer, PPCPs and other potentially

harmful organic compounds may be bound up in the biosolids, which are also potentially transported to surface and groundwater sources during heavy rain.

Wastewater treatment technologies and EPs

As treated wastewater effluent has been identified as a primary source of PPCPs, improving treatment of wastewater is a logical solution to reduce growing quantities of PPCPs in the environment. Because it seems unlikely that the quantities of PPCPs utilised will decrease as rapidly as would be necessary to stop concentrations from reaching harmful levels, options for tertiary treatment of wastewater must be explored and considered (Campbell, et al., 2006).

Conventional treatment of wastewater and drinking water does not seem to be sufficient at this stage; in general, primary treatment by physiochemical methods such as coagulation and flocculation are unable to remove EDCs and PPCPs from effluent streams (Bolong, et al., 2009; Gavrilescu, et al., 2015).

Chlorination has also not been shown to be effective in removing the majority of pharmaceuticals. Activated sludge and other forms of biological treatment have shown varying rates of removal for pharmaceuticals, ranging from less than 20% to greater than 90% (WHO, 2014).

More promising are advanced wastewater treatment processes, including ozonation, activated carbon and membrane nanofiltration and reverse osmosis, and advanced oxidation technologies (Bolong, et al., 2009; Liu et al., 2009). Some of these have been observed achieving removal rates above 99%

Source: Wikimedia Commons

for targeted compounds in the published literature (WHO, 2014). Adsorption by activated carbon and ozone and UV advanced oxidation have been effective in removing some EDCs and PPCPs (Liu et al., 2009). The process works by mineralizing pollutants in wastewater to carbon dioxide, or transferring pollutants to strong oxidizers using oxidation-reduction reactions. However this can be dangerous in some rare cases because oxidation can change previously innocuous compounds into more harmful byproducts (Bolong, et al., 2009). Furthermore, much of the carbon used in this process either ends up in a landfill or needs to be regenerated, a process which uses a lot of energy and indirectly may lead to greater environmental risks (Verlicchi, et al., 2010).

Ultraviolet photolysis has also been considered, but was found to remove only fifty to eighty percent of target compounds even when the dose was over a hundred times a typical disinfection dose (Bolong, et al., 2009).

Efficiency of primary treatment for the removal of pharmaceuticals depends on "operational configuration of the wastewater treatment facility... sludge age, activated sludge tank temperature and hydraulic retention time" (WHO, 2014, p. x), and even studies done on one compound at different locations or different times have produced different results. Type of compound is also important for predicting removal rates; in a review of many recent studies analgesics, anti-inflammatories, and beta-blockers were the most resistant to treatment, while anti-depressants had the highest removal rates (Deblonde, Cossu-Leguille & Hartemann, 2011).

Notably, some compounds that appear to have relatively high removal rates may be absorbed into sludge, meaning that if they are used as fertilizer later they may end up in groundwater or enter the surface waters through runoff. In this sense, measuring concentrations in influent and effluent of treatment plants may not be a true indicator of environmental impact from certain compounds (Deblonde, et al., 2011).

Furthermore, even the most advanced wastewater treatment technology will not be able to completely remove all pharmaceuticals at all times. It is therefore important to consider the costs of these often very expensive technologies relative to the potential toxicity of the compounds they are intended to remove. Using combined analyses and models of PNECs to develop an informed risk assessment is crucial before significant resources are spent on upgrading infrastructure (WHO, 2014).

PPCPs in the Environment

PPCPs have been detected in the environment in increasing quantities around the world. Aus der Beek et al. (2016) carried out a study funded by the German Federal Environmental Agency using a database of published and unpublished literature regarding concentrations of pharmaceutical compounds in the environment around the world. Data showed that pharmaceuticals or transformation products have been detected in seventy-one countries around the world – located in all five of the recognized UN regions.

Five hundred and fifty-nine pharmaceuticals have been detected globally in WWTP effluent, influent, and sludge. Diclofenac was the most commonly detected pharmaceutical. Nearly as common were carbemazepine (an antiepileptic), sulfamethoxazole (an antibiotic), and ibuprofen and naproxen (analgesics). EE2 has been detected in all UN regions, as has the lipid-lowering drug clofibric acid (aus der Beek, et al., 2016).

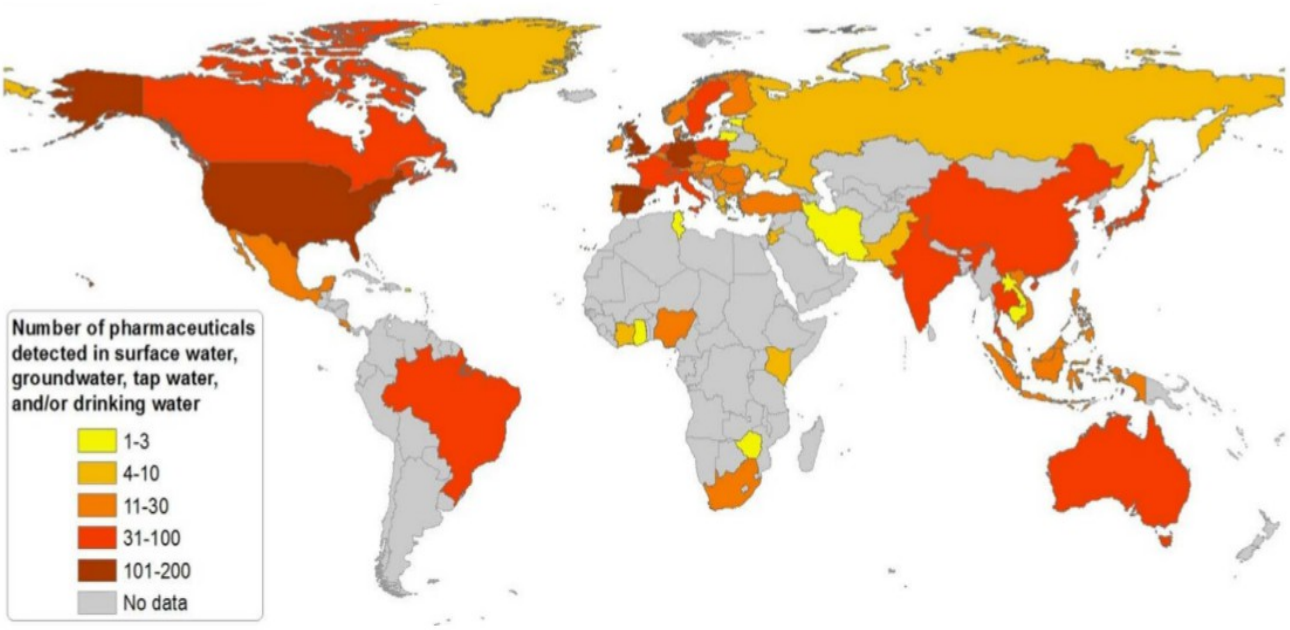


Figure 1. Country survey on the number of pharmaceutical substances detected in surface waters, groundwater, or tap/drinking water (aus der Beek, et al.,2016, p. 829)

Currently it seems that "for most pharmaceuticals, the levels detected in the environment are at least an order of magnitude lower than those levels shown to cause any effect" (Corcoran, et al., 2010, p. 298). There are, however, some notable exceptions to this statement, and concentrations vary greatly both regionally and locally.

In Europe, ibuprofen has been identified at levels well above the PNEC in WWTP effluents, canal water, and rivers, while in North America and Asia the levels are still safely below the PNEC (Pal, et al., 2010). Diclofenac has also been detected in treatment plant effluent and surface waters in the low $\mu g\ L^{-1}$ concentration range, which has been shown to cause toxic effects in laboratory experiments on fish (Corcoran, et al., 2010). Antibiotics like tetracycline, trimethoprim, and ciproflaxin have also all been observed above PNECs in surface and groundwater in Europe and North America.

Concentrations of pharmaceuticals detected in the aquatic environment are impacted by the degree to which they are metabolized in the bodies of target organisms, in addition to their degradation rates and partitioning of the compound in sediments and the water column (Corcoran, et al., 2010). Some pharmaceuticals are partially metabolized in the body of the target, others pass through completely without having crossed the gut wall and are excreted without any change. Concentrations of pharmaceuticals in wastewater also vary seasonally based on temperature, solar radiation, and precipitation rate (Deblonde,et al., 2011).

Source: Pexels.com

Variations have also been observed between areas directly adjacent to WWTPs, hospitals, and industrial pharmaceutical production facilities (Verlicchi, et al., 2010). The significant exposures experienced by organisms in close proximity to these point sources raises concerns about both acute and chronic toxicity. Conversely, organisms in areas with relatively low levels of pollution may be at greater risk to new exposure because they haven't built up any sort of prior resistance (Daughton & Ternes, 1999).

Policies and regulations

There has thus far been minimal policy response to EPs. Existing rules on wastewater treatment, drinking-water standards, and toxic substances can be used to manage EPs under a broader umbrella, but "there is little evidence in the legal literature of any state or jurisdiction (in the EU, US, or elsewhere) making comprehensive provision for the management of pharmaceuticals or other [contaminants of emerging concern" (Hendry, 2017). The following section will discuss some of the frameworks, directives, and policies that have been applied to EPs in Europe, the United States, and internationally.

"There is little evidence in the legal literature of any state or jurisdiction (in the EU, US, or elsewhere) making comprehensive provision for the management of pharmaceuticals or other CECs" (Hendry, 2017).

Europe

In 2011, the EEA did a study of 'hazardous chemicals of concern', followed by an EEA Joint Research Council (2013) report on the relationship between environment and human health. They concluded that these challenges require systematic policy solutions in addition to those already in place (Hendry, 2017). Currently, the European Union has a number of policy documents relevant to the monitoring and regulation of EPs. Among these are the Bathing Water Directive (BWD), Drinking-water Directive (1980), Urban Wastewater Treatment Directive (1991), and the Water Framework Directive. The Water Framework Directive defines annual average and maximum allowable (short-term, immediate) limits to concentrations of priority substances, and has a focus on supporting aquatic life and biological assessment including diversity, distribution and age of fish populations. As such, the EEA considers this series of directives to be the "Overarching mechanism for addressing the wider impacts of contaminants of emerging concern (CECs) on the aquatic environment" and the "obvious vehicle for managing risks of CECs in the environment" (Boxall, 2011).

The EU Water Framework 2000/06/CE Annex X was updated in 2000 to include a "list of 33 priority substances or groups of substances which include metals, pesticides, phthalates, polycyclic aromatic hydrocarbons, and endocrine disruptors. These items must be removed with an objective of quality and preservation of good ecological status by 2015" (Deblonde, et al., 2011, p. 442). There are also abatement measures outlined in the "Integrate Pollution Prevention and Control" directive. The priority substances directive (PSD) (European Parliament Council, 2008a, 2013) works in conjunction with other legislation. The directive has not yet been amended to include many EPs or set more stringent limits, in

part because this would have implications for the nature and extent of wastewater treatment required of cities under the Urban Wastewater Treatment Directive (Hendry, 2017). It is also important that approval of new pharmaceuticals on the market "...be better coupled with meaningful ecological risk assessments (and followed up with confirmatory environmental survey [environmental risk assessment] studies after market introduction" (Daughton & Ternes, 1999, p. 911).

Source: Darwin Bell via Wikimedia Commons

In terms of response to EPs, the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation (European Commission, 2006) is of particular importance. REACH led to the establishment of the European Chemical Agency. The regulation explicitly states that burden of proof that a compound is safe lies with industry, and thus makes companies responsible for management of risks and provision of safety information. For a new chemical to come onto the market, companies must perform varying levels of aquatic toxicity testing under REACH. Base-set testing for chemicals produced or marketed at over 10 tonnes per year requires acute toxicity tests on fish, algae, and a crustacean. Companies must determine the concentration that kills or has an effect on 50% of organisms and make this information public. For chemicals produced or marketed at less than 100 tonnes per year, acute toxicity information is sufficient.

Source: Wikimedia Commons

For chemicals with more than 100 tonnes the regulation requires study of more subtle effects (ie. vitellogenin induction, impaired growth of juveniles, reproduction, multigenerational survival) using testing methods standardized by the OECD (Boxall, 2011). It also calls for progressive substitution of most dangerous chemicals when safe alternatives have been identified (Boxall, 2011). It is notable, however, that

none of these regulations or frameworks is specifically designed to target PPCPs, though the potential for EP ecotoxicity, persistence, and accumulation means that they are candidates for inclusion.

The United States

In the United States, the Clean Water Act of 1972 includes provisions for the proper management and disposal of wastewater, and the Resource Conservation and Recovery Act of 1976 manages hazardous substances and waste. Similar to the Water Framework Directive in the EU, the Clean Water Act has been interpreted as applying to EPs, but it does not explicitly set out standards for most pharmaceuticals. The Food and Drug Administration does have requirements for environmental fate and effect of drugs sold in the United States, which were introduced through the National Environmental Policy Act of 1985. This was followed by an environmental assessment technical handbook (1987) and a guidance for industry for the submission of an environmental assessment for human drug application and supplements (1995) (Halling-Sorenson, et al., 2010).

Spotlight on Action: Microbeads

Microbeads provide an interesting example of what can happen when a public consensus is reached that a substance in PPCPs is more harmful than helpful. Microbeads are tiny plastic particles that are often used in exfoliating facial and body scrubs and toothpastes. These minuscule particles are small enough to pass through wastewater treatment plants and into surface waters, where they have a tendency to absorb hazardous chemical pollutants. When fish mistakenly consume them after confusing them with plankton or other food sources, they are at risk of a wide array of toxic effects. In December 2015 the United States government put in place a ban on microbeads that requires manufacturers to stop use of microbeads in products by July 2017 and end their sale by July 2018. The Canadian Environmental Protection Agency has added microbeads to a list of toxic substances in 2016, allowing government to regulate and ban use of microbeads. In September of 2016 the government of the United Kingdom also announced plans to ban microbeads in cosmetics and personal care products, although this has been disputed in the European Union because of its potential to conflict with free trade agreements. Luckily it seems that many companies are willing to comply with voluntary agreements to remove microbeads from their products in the EU by 2020; they know that consumers prefer products without microbeads and are responding to a demand for more environmentally safe products.

Source: Wusel007 via Wikimedia Commons

International frameworks

Effective management of EPs is important for the realization of several of the Sustainable Development Goals, including SDG 3 (ensure healthy lives and promote well-being for all at all ages), SDG 6 (ensure availability and sustainable management of water and sanitation for all), and SDG 12 (ensure sustainable consumption and production patterns).

Several existing international agreements either directly or indirectly address EPs and PPCPs. UN Environment is responsible for three related global 'chemical conventions': The Basel Convention on Transboundary Management of Hazardous Waste (1989), the Rotterdam Convention on the prior informed consent procedure for certain chemicals and pesticides in international trade (1998), and the

Stockholm Convention on Persistent Organic Pollutants (2001). Other important agreements include sound management of chemicals as was mandated in the Johannesburg Plan of Implementation (UN, 2002), and health and safety regulations, such as the International Labor Organisation conventions on safety in the use of chemicals at work (1990). Each of these addresses a different piece of the complex puzzle involved in successful management of EPs.

Policy initiatives like the strategic approach to international chemicals management (SAICM), also play an important role. SAICM was adopted with the agreement of 140 countries, and has since adopted resolutions on endocrine disruptors, nanoparticles, and chemicals in products. They are currently considering impacts of pharmaceuticals.

Spotlight on Action: The Stockholm Convention

The Stockholm Convention is a global treaty signed into effect in 2002 with the goal of protecting human health and the environment from persistent organic pollutants (POPs). Parties to the convention are expected to eliminate or restrict the production and use of POPs.

Originally the convention named twelve 'dirty dozen' contaminants to target, and over time more have been added. EPs and PPCPs are not all persistent, which means they cannot all be covered by the Stockholm Convention, but as the knowledge base from research continues to grow, more pharmaceutically active compounds will likely be included under this important international agreement.

At the regional level, UN Economic Commission for Europe (UN/ECE) manages the Geneva Convention on Long Range Transboundary Air Pollutants (UN/ECE, 1979). This includes a protocol on persistent organic pollutants, which was originally written with the intention of dealing with acid rain, although many EPs qualify as hazardous substances so the framework is relevant to their management. The UN/ECE has a globally harmonized system of classification and labeling of chemicals (2003) open to all states. Regular revisions of this system enable management of new compounds and newly recognized effects.

What can be done?

Source: Pexels.com

Research on impacts and toxicity

Because not much is known about specific impacts o
PCPPs in the environment it would be wise to behav
cautiously. However, the costs of removing
pharmaceuticals from wastewater, or from banning
without a reliable substitute, can be quite high. Mo
needed if we are to take meaningful action towards addressing the impacts of emerging pollutants without overreacting to chemicals and compounds that may not actually cause significant harm. There is limited information about realistic effects of EPs at their current concentrations in many locations. Many studies have detected pharmaceutical compounds in municipal wastewater and effluent; however it is currently very difficult to compare data between locations or over time because studies have been somewhat ad hoc in most cases. There is not a standardised system for testing drinking water or other water for the presence of pharmaceuticals (WHO, 2014).

Laboratory based testing of EPs tends to look at acute exposure to much higher levels of the compounds than have been observed in surface or drinking waters *in situ*, and PNECs often do not take into account long-term or chronic exposure to the miniscule quantities of PPCPs that have been detected thus far in the environment (Gavrilescu, et al., 2015). A further limitation is that measurement of specific compounds does not provide information about synergistic or antagonistic interactions between multiple compounds (Campbell, et al., 2006). Moving forward, it will be important to "...move beyond the piecemeal, one chemical at a time, one disease at a time, one dose approach currently used by scientists studying animal models, humans, or wildlife" (Bergman, et al., 2013, xv).

One way to do this is to use biologically based assays - a method of measuring a known response to the presence of EPs - rather than seeking out the compounds themselves in the environment (Campbell, et al., 2006). This provides a potentially more cost-effective and efficacious alternative to monitoring specific priority substances, which may miss other, as yet unknown compounds and minimize the relevance of mixtures (Boxall, 2011). Quantitative structure-activity relationship (QSAR) models can also help to fill gaps in knowledge of toxicity of specific compounds by correlating biological activity with chemical structure using an 'effect and probable cause' model (Boxall, 2011). Multi-substance 'potentially affect fractions' (msPAF) can be combined with an estimate of how many species are sensitive to organic toxicants in an aquatic ecosystem. This translates into a model based on mixture toxicity and specific sensitivity distributions that should account for bioaccumulation and biomagnification so cumulative impacts can be assessed. These assessment and modeling tools can be

used to help link contamination with deterioration of ecological quality and evaluate existing chemical and biological monitoring data with site-specific experimental techniques to establish cause- effect relationships (Boxall, 2011).

The list of EPs is continuously expanding, creating new and unique challenges with every new innovation. For nano-materials, microplastics, and ionic liquids for example, methods for sampling and environmental analysis are basically non-existent (Geissen, et al., 2015). As these things become more common these issue become ever more pressing. Nano-materials, for example are being included in cosmetics, therapeutic drugs, detergents, and more, and there are estimates that three to four new consumer products using nano-technology are coming onto the market every week (Ray, et al., 2009). Governments and international organisations should provide support for research to promote informed decision making and reduce the likelihood of toxic effects from EPs.

Improved monitoring

Knowledge is limited regarding the current prevalence of EPs. EPs have been found in surface waters, sewage sludge, sediment, and marine biota in locations ranging from industrialized areas in Europe to the remote Arctic. Despite mounting concerns about their impacts, EPs are largely not included in regular and standardized monitoring programs. Adding some emerging pollutants to priority standards lists for targeted monitoring could lead to more timely awareness of potentially problematic substances that may need to be regulated (Boxall, 2011). The focus here should be on pharmaceutical compounds that are used at particularly high doses, are likely to bioaccumulate, have a high potential for triggering systemic allergic responses, or have a therapeutic dose at or above a toxic dose (Pal, et al., 2010).

Unfortunately at this time, although there have been studies on EPs in the environment done in every region of the world, more than three quarters of them have been in Western Europe, North America, Australia, or New Zealand. Of seven hundred and thirty articles considered by aus der Beek et al. (2016) 221 were from Germany, 143 from the United States, and 83 from Spain. Only twenty-three relevant studies were found for the entire African continent, predominantly in South Africa, Nigeria, and Kenya (aus der Beek, et al., 2016). This regional bias can lead to underestimation of the potential impact of EPs in regions where less studies have been carried out so far.

Where monitoring has been done, notable regional differences in what compounds were found have been observed. Some antibiotics, veterinary growth stimulants, and antiviral substances were detected in Asia and Africa that have never been detected in Western Europe and Others (aus der Beek, et al., 2016). This may in part be because of regional biases toward measuring specific therapeutic groups. An emphasis on detecting certain classes of compounds can lead to false assumptions that, for example, estrogens are the most common pollutant in Africa, when in reality they are simply the most studied (aus der Beek, et al., 2016).

Researchers are aware that increased detection of EPs in the environment is at least partly due to improvements in detection technologies, rather than rapid increases in their quantity (Hendry, 2017). In regions where laboratories have limited capacity to perform the highly specific tests needed to detect PPCPs, it is difficult to know whether potentially toxic compounds are present. Particularly in Latin America and the Caribbean, a very small number of studies have been published thus far, and support for capacity building and technology transfer could significantly increase the ability of many countries to carry out monitoring activities.

The lack of data for densely populated areas in Latin America, Asia, and Africa is concerning. Many pharmaceutical manufacturers are located in these areas, and as consumption and availability of PPCPs grow, questions of both point-source and diffuse pollution are emerging significant issues (aus der Beek, et al., 2016).

Long-term monitoring data is scarce; there is a gap in our knowledge concerning seasonal and annual fluctuation data. In addition, not all existing data is good. There is a bias towards sampling near hot spots or existing monitoring stations that might not be particularly relevant, and many studies dealing with EPs have been published in analytical chemistry journals which might be more interested in developing methodology over representative sampling.

In 2005 the EU made a major step towards improved monitoring of EPs by establishing the NORMAN Network of reference laboratories, research centres and organizations focused on expanding knowledge of pathways, occurrence, fate, and impacts of EPs (Hendry, 2017). They have also funded the Knowledge and Needs Assessment of Pharmaceutical Products in Environmental Waters (KNAPPE, 2008) project. More regions around the world will need to support similar widespread monitoring projects if the extent of contamination from EPs is to be more fully understood.

Behaviour change and awareness raising

Addressing the challenges posed by emerging pollutants will require a wide array of solutions. One approach is to try to raise awareness about appropriate disposal methods. Another is to tackle inappropriate and excessive consumption of PPCPs, thus reducing amounts produced and released into the environment using targeted information campaigns and awareness raising activities. These campaigns can aim at, for example, unnecessary prophylactic use of antibiotics for humans and domesticated animals, or use of PPCPs in excess of recommended dosages (aus van der Beek, et al., 2015).

One example of how this can work is an innovative programme in Sweden aimed at empowering patients and consumers to make informed decisions about their pharmaceutical consumption. The pharmaceutical industry worked with the government to compile advice to consumers and medical professionals about choosing drugs with the smallest possible environmental impacts. For example, a patient choosing a painkiller can now be informed that they have an option to select a less environmentally persistent drug if they avoid the anti-convulsant carbemazepine (Lubick, 2010). For veterinary pharmaceuticals in the United Kingdom there is also a programme called the UK

Veterinary Medicine Directorate Suspected Adverse Reactions Reporting Scheme. Projects like this are rare, and comprehensive information about fate and effects of pharmaceuticals in the environment is not frequently publicly available (Boxall, et al., 2012).

Spotlight on Action: Pharmaceutical Take-Back Programmes

Programmes that provide opportunities for safe disposal of unused pharmaceuticals are an important way to prevent them from being flushed down the toilet or sent to landfills where they can potentially leach out into surrounding groundwater or surface waters. In Europe and Canada standardized pharmaceutical take-back programmes have existed for decades. Some companies provide pre-paid envelopes or host collection days, and organizations in the United States and elsewhere aim to raise awareness about how to safely dispose of unused or expired pharmaceuticals (Lubick, 2010).

Industry support for addressing the growing problems with EPs should be promoted and encouraged. Incentives are needed for sustainable consumption and production, such as 'green chemistry' approaches and technologies that maintain quality of a product while reducing or eliminating use and generation of hazardous substances (Boxall, 2011).

One way to do this is to minimize the use of water and other solvents in production processes. Another is to move towards the most pure possible forms of medications. Currently drugs often include chiral mixtures,with both the primary active form of a compound and the mirror image of that compound, which may have no effects or even harmful side effects. Effectively producing the purest forms of some compounds would mean reducing doses of many medications by up to fifty percent. This would then reduce the amount of pharmaceuticals released into the environment, while minimizing harmful side effects for patients (Daughton & Ternes, 1999). Someday it may even be possible to target prescriptions to a patient's specific genome, to maximize efficiency and minimize excretion (Daughton & Ternes, 1999).

Pharmaceutical companies could be encouraged to sell their products in smaller package sizes and give out less samples, thus decreasing the amount of drugs that are purchased and never used. The number of drugs, particularly those with potential ecotoxicity, sold over-the-counter without a prescription could be limited. Illegal drug use and traffic in counterfeit - often substandard – pharmaceuticals should also be addressed. Illicit drugs like cocaine have been detected in water supplies in many urban areas and their impacts on wildlife are not well understood.

Information on prescription drug consumption, production, and prescription is difficult to obtain or confidential in many countries, and if industries could be enticed to contribute to national databases it would support more informed decision making on the part of legislators and policy makers (aus van der Beek, Weber & Berman, 2015). Countries and companies that successfully implement EP monitoring or treatment projects, adoption of pollution prevention policies, and cleaner production policies, should be encouraged to

promote information sharing and transfer of best environmental practices and best available techniques.

Challenges to action

There are several factors limiting our ability to respond quickly and comprehensively to the challenges posed by EPs and PPCPs. First and foremost, pharmaceuticals are crucial to maintaining our current health and quality of life. Any attempt to regulate or restrict pharmaceutical use must take that into account, and be careful not to do more harm than good. But hesitance to impose regulations on pharmaceutical companies can also make it more difficult for governments and other actors to take action; without regulations or even guidelines it may be difficult to know where to begin.

Removing EPs from wastewater can also be a costly endeavor. Upgrading WWTPs is expensive. Recommendations about the most effective and affordable techniques for removal would be useful; however even the best current technologies cannot remove all EPs at all times. Focusing on one compound at a time is impractical when mixtures of compounds could be far more dangerous than any individual EP. A lack of standardized monitoring strategies worldwide and case-by-case approach to studies of impacts from PPCPs mean that there is no universal understanding of which wastewater treatment methods are 'best', or which EPs are 'worst'.

Furthermore, development of new chemicals has outpaced the ability of governments to respond. The continually expanding range of compounds that qualify as emerging pollutants means that the current ad-hoc method of testing and regulating one at a time is simply not able to keep up.

Regulatory Challenges: Ethinyl Estradiol

Ethinyl Estradiol (EE2), the active ingredient in most birth control pills, was introduced in the box on page 5 (A household compound with unexpected consequences). Due to its well documented impacts on the environment and potential effect on human health, in 2012 European Commission proposed it as an EU-wide priority substance for monitoring and eventual removal. However, inclusion of EE2 has been delayed, and some researchers believe that this is largely because costs of control will be so high (Owen & Jobling, 2012). An article published in the journal Nature estimated that the price tag of removing EE2 completely from wastewater in England and Wales could be as much as thirty billion pounds. Their estimates were done using a form of activated carbon which is quite expensive, but whatever strategy is used the costs will undoubtedly be quite significant.

Furthermore, it is unlikely that restrictions on consumption of EE2 will be successful. Access to birth control pills could be viewed as a political issue, or an attempt to infringe on women's right to control their fertility. Until reasonably affordable options are proposed for either removing EE2 from wastewater or replacing it with an equally effective alternative, it seems unlikely that most countries will be able to reduce concentrations in the environment.

Conclusion

Emerging pollutants, and PPCPs in particular, are a growing challenge for scientists and policy makers. Awareness is growing that these compounds are increasingly ubiquitous in waters around the world. While there is a general consensus on the fact that action should be taken, more information is needed to identify the most cost-effective and efficient methods of minimizing, mitigating, and preventing the potentially damaging impacts of PPCPs on wildlife and humans.

Source: Maxpixel

Some areas are at greater risk than others. Densely populated cities where waste flows directly into nearby surface waters are at great risk, as are developed nations where pharmaceutical use is significant and growing rapidly. Even in remote areas, however, there is a potential for exposure to EPs. The persistent nature of many compounds means that they can be transported over long distances, and a diverse array of harmful substances disproportionate to the amount consumed locally have been reported in ecosystems of small island developing states. This is true of PPCPs, microplastics, heavy metals, and more (UNEP, 2014).

Climate change may also lead to changes in distribution and effects of EPs. In areas with more intense rainfall, the frequency and severity of polluted urban storm flows is expected to increase. Flushing to water bodies of organic pollutants will likely increase along with it. Hot, dry summers and droughts will decrease river flow, reducing contaminant dilution capacity and elevating concentrations in some areas (Boxall, 2011).

It is likely that newly developed technologies will have both positive and negative impacts in this field. Companies are working to produce more 'pure' forms of drugs with only the desired enantiomers. This will make drugs more effective at lower doses and less active pharmaceutical ingredients will be excreted into wastewater. It will also mean that lower detection limits will be needed, as lower doses will potentially grow more potent, with greater environmental impacts. Cutting edge nano-technologies

promise exciting improvements in health and other fields, but their impacts on the environment are still not well understood.

At this stage, expansion of research and improvements in monitoring capacity are the most important actions needed to address EPs. Comprehensive policies and regulations can then be developed to prevent harm from the most dangerous EPs, particularly to vulnerable populations. The precautionary principle should be emphasised, but only in careful and evidence-based ways. We must do our best to respond to EPs, while avoiding undue or unnecessarily expensive burdens on communities that are only now beginning to realize the benefits of PPCPs for human health and well-being.

Source: MaxPixel (http://maxpixel.freegreatpicture.com/Splash-Clean-Water-Rain-Blue-Liquid-Drop-Clear-880462)

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