Impacts, Management and Policy Recommendations Related to Pharmaceuticals in the Canadian Aquatic Environment

By

Oluwatosin Joseph Aladekoyi (PhD cand., MASc., MSc., B.Sc.)

A policy brief submitted

In fulfillment of the requirements of the

Geoffrey F. Bruce Fellowship in Canadian Freshwater Policy 2022/2023

October 2023

Acknowledgement

I am very grateful to the Geoffrey F. Bruce Fellowship in Canadian Freshwater Policy which generously provided financial support for the policy focus in my PhD studies. The funding provided through this fellowship allowed me to invest more time during my PhD research to help advance research related to water policy. This funding has also contributed to my ability to obtain a research related position with Environment and Climate Change Canada directly related to my research which I hope will advance policy related to pharmaceuticals and other chemicals of emerging concern to protect freshwater systems in the future.

Introduction

Water has been referred to as the 'gold of the 21st century' (Farrell, 2012) and this is due to the high negative pressure that is being exerted upon the quality of water sources by anthropogenic contaminants, commonly known as contaminants of emerging concerns (CECs). These contaminants are released into the aquatic environment from various sources and the ecological impacts that they have on the environment and aquatic health is a challenge that both developed and developing countries are facing (Ebele et al., 2017). This paper focuses on a group of such contaminants known as pharmaceuticals (also referred to as pharmacologically active compounds, PhACs).

PhACs are prescription, veterinary, and over-the-counter medications for humans and animals (Ebele et al., 2017). They continue to gain the attention of both scientists and policymakers, not just because of their presence in receiving waters at different concentrations (Metcalfe et al., 2001), but the impact that they have on aquatic health (Ebele et al., 2017; Tehrani & Gilbride, 2018). They enter the environment through different routes such as human consumption, excretion, and improper discharge down the toilet into the sewers (Angeles et al., 2020), agricultural runoffs (Archer, Petrie, et al., 2017), improper disposal to landfills where they leach into water sources (Pollution Probe, 2019), healthcare facilities, and pharmaceutical industries (Kleywegt et al., 2019). Though these PhACs are released from different sources and follow different routes to enter receiving waters, the wastewater treatment plant (WWTP) remains their main route of entry into the environment. Since the WWTP's primary design is not to eliminate micropollutants such as PhACs, they easily bypass the treatment process and are discharged into the aquatic environment where they give rise to other issues.

Brief History of the Presence of PhACs in the Environment

Before the science about the effects that PhACs could have on the environment became more pronounced in recent years, the research surrounding their presence in the environment dates back to the 1970s when researchers were becoming concerned about their presence in effluents that were leaving the WWTPs for receiving waters (Tabak & Bunch, 1970; Hignite & Azarnoff, 1977). About 20 years later, technological improvements and the development of analytical equipment steered experimentations towards the possible detection of microcontaminants, including PhACs, at nanogram per litre (ng/L) concentrations (Daughton & Ternes, 1999). The ability to detect PhACs at these very low concentrations further raised interest and questions amongst scientists, policymakers, and regulators about whether these PhACs warrant further studies or whether they could have a potential impact at such low concentrations. But considering that PhACs are designed to demonstrate specific biological at low concentrations, more experiments are being carried out to better study and understand them. For example, in the first two months of 2009 than in all of 1997, there were more documents published on PhACs in the United States Environmental Protection Agency (USEPA) bibliographic database (Daughton, 2009).

Research has since then increased, not only focusing on the occurrence of PhACs in different regions around the world but also their occurrence in several environmental matrices (Agunbiade & Moodley, 2014; Archer, Petrie, et al., 2017; Loos et al., 2013; C. Metcalfe et al., 2004). PhACs have been reported in matrices such as drinking water (Metcalfe et al., 2004), groundwater (Sacher et al., 2001), soil (Kołecka et al., 2019), sediment (Blair et al., 2013), and freshwater sources (Bound et al., 2006; Kolpin et al., 2002; Petrie et al., 2015). Their presence in virtually all matrices attests to their prevalence in the environment and the potential effect that they may have on aquatic health.

It is noteworthy that PhACs are not the only contaminants present in the environment as there are several chemicals from industrial and domestic sources present in effluents reaching receiving water. While it could be argued that any of those chemicals could be responsible for observed ecological impacts, the impacts that PhACs can have on aquatic organisms should not be undermined. Research has shown that some of these ecological impacts significantly correspond to those that could be caused by the

pharmaceutical compounds that are released into receiving waters from different effluents (Metcalfe et al., 2001).

The Ecological Impacts of PhACs on the Environment

The problem with PhACs goes beyond their mere occurrence in the environment as their presence in the aquatic environment has been linked to different ecological problems. Though PhACs are known to be present in the environment at low concentrations, their ability to persist in the environment is one of the major reasons that makes them a concerning group of contaminants. This means that they have the potential to withstand photodegradation (degradation by sunlight) or biodegradation (degradation by microorganisms). Despite that not all PhACs possess properties that make them persistent, the fact that they are being continually used and discharged into water sources gives them a pseudo-persistent property (Ebele et al., 2017).

Due to their ability to remain in the aquatic environment for a longer time (Williams et al., 2016), PhACs can bioaccumulate in the tissues of aquatic organisms such as mussels, fish, shrimps, and other organisms that are known to serve as food sources to humans. These bioaccumulation factors are known to be quite high in some cases. For example, PhACs have been reported to be present in organisms such as periphyton up to 4.7 μg/L and up to 24 μg/L in snails (Vernouillet et al., 2010) and they can also bioaccumulate with bioaccumulation factor up to 3000 in snail (Du et al., 2015). What this bioaccumulation factor means is that, if PhACs were reported to be present in the water at 1 ng/L, which is very low, they can be present in the tissues of organisms living in that water at 3000 ng/L, which is significantly higher than the concentration of the organism's environment.

Another important concern is what is often referred to as synergistic effects, which is the effect that the mixture of two or more PhACs could have on aquatic organisms by interacting together to elicit a negative response in them. The issue is that many studies have focused on the individual effects of PhACs on selected organisms but only a few studies have examined the effects of mixtures of PhACs despite that the synergistic effects more closely reflect the reality of what happens to aquatic organisms when they are exposed to cocktails of pharmaceutical compounds. There have been reports showing how the mixture of PhACs caused a negative reaction in aquatic organisms, such as altered embryo production and reduced fertility in fish, but when the same organism was exposed to the compounds separately, the same effects were not observed (Galus et al., 2013). The fact remains that contaminants interact together in the environment but this is not well understood, and this is one of the reasons why the synergistic effects of PhACs remain a knowledge gap that is yet to be filled in this research area, warranting further study.

Another reason why the presence of PhACs in the environment is very concerning is because of their ability to disrupt the endocrine system pathway of non-target organisms such as fish (Archer, Wolfaardt, et al., 2017). An endocrine-disrupting chemical, as defined by USEPA, is a chemical that alters the synthesis, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behaviour, and reproduction (USEPA, 1997). Drugs like hormones, glucocorticoids, and non-steroidal drugs are known to be among the categories of drugs that cause endocrine disruption in aquatic organisms. For example, estrogens have been reported to have the potential to induce intersex in fish (Metcalfe et al., 2001).

The uncontrolled and extensive use of antibiotics in the treatment of human and animal infections has been reported to contribute to the prevalence of antibiotic-resistant bacteria (ARB) and antibiotic-resistant genes (ARGs), making it more difficult to treat infections and diseases (Archer, Petrie, et al., 2017; Ebele et al., 2017; Islam & Gilbride, 2019). Antibiotic resistance continues to gain significant attention as a public health concern because each year, there is an increase in the number of drugs that are no longer effective in treating diseases. Anderson et al. (2019) argue that by 2050, all the drugs that are currently effective in treating infections and diseases might no longer be effective because of antibiotic resistance, a state the authors referred to as "a therapeutic deadlock".

The Management of PhACs in Canada

Are discussions concerning the impacts of PhACs on the aquatic environment exaggerated? Are there management measures in place to address the problem? Are these measures effective? Are there consequential impacts on humans or is it time to move on to other contaminants that are more concerning? These are part of the questions that continue to persist regarding the presence of PhACs in the environment and their impacts on aquatic organisms. While there are a lot of publications in this research area, some key knowledge gaps continue to remain and part of what has been reported in science has not been translated into effective policy or regulatory options yet in Canada (Kingsmore, 2013; Pollution Probe, 2019). For example, there is a legislative gap in the regulation of PhACs in wastewater effluents that are discharged from WWTPs, pharmaceutical industries, and healthcare facilities (Pollution Probe, 2019). Though there are regulations for more common contaminants, they do not include CECs like PhACs. For example, the Ontario government, through the use of regulated effluent limits in Environmental Compliance Approvals (ECAs), and the federal government, through the Wastewater Systems Effluent Regulation (WSER), both regulate the effluent discharge from wastewater treatment plants into receiving water bodies (Kleywegt et al., 2019). However, these regulations do not monitor or control PhACs but are primarily used in monitoring and controlling conventional parameters such as biochemical oxygen demand, unionized ammonia, suspended solids, total residual chlorine, organics, metals, and nutrients (Kleywegt et al., 2019).

A similar scenario also applies to wastewater from healthcare facilities and PhAC industries. For example, in Ontario, wastewater effluents that are discharged from manufacturing industries and healthcare facilities are regulated by municipalities under the sewer discharge bylaw where each municipality sets the approved discharged limits for each facility that discharges through the sewer to the WWTP. However, these limits only address conventional parameters like metals, organics, and pH. They do not contain specific limits for CECs like PhACs but allow chemical manufacturing industries like the PhAC industry to discharge their effluents directly into the sewers for WWTPs which are also not designed to eliminate them from effluents.

Scientific uncertainties make management and regulatory options difficult

Despite all the ecological impacts that the presence and persistence of PhACs could have on the aquatic environment, it is only logical to wonder why it looks like the government is not regulating the discharge of pharmaceutical effluents from industries to WWTPs or from WWTP effluents to receiving water bodies. The answer to that might appear simple yet complicated: there are scientific uncertainties that continue to remain in the research area which creates a knowledge gap. One of the gaps is that there seems to be dissension amongst scientists about whether there is a need to even worry about the presence of PhACs in the environment as they do not agree on the perceived ecological impacts that PhACs are said to have.

While some scientists agree that the presence of PhACs in the aquatic environment could have a potential impact on aquatic health and justify the need for further research (Archer, Petrie, et al., 2017; Du et al., 2015; Metcalfe et al., 2001; Vernouillet et al., 2010), others think that the impacts that they have are very low and exaggerated (Johnson & Sumpter, 2016; Richardson & Bowron, 1985). For example, for a long time, researchers have worried whether these reported aquatic health impacts could also affect humans if they consume environmentally relevant concentrations of the contaminants (that is, concentrations of PhACs commonly reported in the environment) in their drinking water, but Richardson & Bowron, (1985) argued that it is difficult to detect any observable effect on humans that will warrant public health concern. The authors posited that this is because the concentrations of PhACs present in drinking water is so small that if humans were to consume drinking water contaminated by environmentally relevant concentrations of PhACs throughout their entire lifetime, they would have only consumed what is recommended for a single dosage.

While their argument might be true, it is also important to note that the absence of scientific proof that there are health impacts on humans does not directly equal a lack of impact. What this means is that

the fact that PhACs are present in low concentrations that may not trigger an acute health effect does not mean that the possibility of a chronic effect being triggered over time could be ignored. The authors also introduced a caveat to their arguments for cases where there are vulnerable persons in the community, who may respond differently, even to the low concentrations. These vulnerable individuals include young infants or fetuses who may be exposed to more concentrations of pharmaceutical compounds presented in the milk or transferred across the placenta of a mother on a prescription drug. Another vulnerable set of individuals to consider are those with drug allergies who may react differently than those with normal non-allergic physiology, or those with enzyme deficiencies who lack specific enzymes such as monooxygenase or dehydrogenase which are required for drug metabolism in the body. Also, when direct effects cannot be seen, indirect effects of PhACs like antibiotic resistance may continue to remain an issue, even for humans and this only shows that this should be seen as a public health concern that warrants further attention, not dismissal.

To further discuss scientific uncertainties, some scientists argued that most laboratory experiments carried out to study the impacts of PhACs on aquatic organisms are neither valid nor reproducible. Salkind (2017), in his book "Exploring Research" referred to this as the lack of external validity. External validity refers to the extent to which the results of a study of an original sample can be applied (generalized) to another sample, and by extension, to the population from which the sample was collected for the experiment. In this light, the experiment carried out by some scientists has been said to not directly mirror the reality of what occurs in the environment. For example, Sumpter & Harris (2016) argued that the fact that a drug was reported to have an impact on an organism studied in the laboratory does not mean that there will be any observable effect if the same study was done on-site (in-situ), that is, in the original habitat where the organism lives. They also noted that prediction models done at an individual level in the laboratory do not reflect what goes on at the population level.

This scientific dissension and lack of certainty make it more difficult for policymakers to come up with an effective framework that will protect the environment. Policymakers use science to develop policies but if the science around an issue is not coherent and consistent, it becomes difficult to develop or implement policy or regulatory options that will address the problem. However, it is irrefutable that there is enough information published in scientific literature to show that PhACs is a valid threat to the aquatic environment and that there is a need for appropriate management option to address the problem. The absence of absolutes while discussing the impacts of PhACs does not mean there is no need to take precautionary measures that will protect the environment. The precautionary principle states that measures that will prevent environmental degradation should not be postponed due to a lack of absolute scientific evidence (Kriebel et al., 2001). Therefore, while the full extent of effects on aquatic organisms and potential impacts on humans remains uncertain, there is no imperative to defer management actions. Implementing regulatory limits on releases from drug manufacturing industries, and healthcare facilities, and enhancing treatment options at wastewater treatment plants should not be delayed pending absolute clarity in the scientific understanding. These actions should be put in place to reduce the rate at which the PhACs end up in the environment.

The Chemical Management Plan As a Management Option in Canada

Notably, Canada has taken some precautionary measures to protect the environment from chemicals that are being used and released into its environment. One of those measures birthed the Chemicals Management Plan (CMP). Under the *Canadian Environmental Protection Act* (*CEPA*), a 7-year mandate was given to the Government of Canada to categorize all the 23,000 chemicals that were documented in the Domestic Substances List. This list contains the names of all the chemicals that were manufactured, imported to, or used in Canada on a commercial scale between 1984 and 1986. In 2006, about 4,300 chemicals out of the 23,000 were categorized as substances of priority, based on the requirements highlighted in the *CEPA*. To meet the standard that qualifies a chemical to be listed as a priority substance, the chemical must be able to persist in the environment, bioaccumulate, and be

inherently toxic to humans and non-human organisms in the environment. Completing this categorization. Canada became the first country to systematically examine all domestic chemical substances known to be in the market (Government of Canada, 2007) and this is a great achievement as it sets the platform for what will follow in the CMP. The CMP was put in place because once the categorization was completed, there was a need for further assessments to be carried out on the priority substances.

In 2006, the CMP was launched as a science-based initiative that is designed to protect the environment and human health by assessing the risks associated with the priority chemicals substances. The initiative is jointly delivered by Environment and Climate Change Canada (ECCC) and Health Canada under the *CEPA* and its overall goal is to assess the environmental and human health risks posed by the 4,300 chemical substances and implement risk prevention or mitigation strategies using the appropriate legislative tools. These tools include legislation like *CEPA*, the *Pest Control Products Act (PCPA),* the *Canada Consumer Product Safety Act (CCPSA),* the *Food and Drugs Act (F&DA)*, the *Hazardous Products Act (HPA*), and the *Fisheries Act (FA)*.

Some of the objectives set out in the CMP are to (1) enhance research, monitoring, and surveillance of chemicals, (2) set priorities and timelines for action on chemicals of concern, (3) increase stewardship and responsibility for substances, and (4) communicate the potential risks of chemicals substances to Canadians. The activities of the CMP cover a wide range including risk management, risk assessment, stakeholder engagement and risk communications, compliance promotion and enforcement, and policy and program management (Health Canada and the Public Health Agency of Canada, 2020).

Screening of PhACs under the CMP

In 2015, 28 priority pharmaceutical compounds were assessed under the CMP as they had been previously identified to be of potential concern to the Canadian environment or human health. These PhACs are used to treat human and animal diseases and are also used in medical research (Government of Canada, 2015). The categories and names of PhACs screened include antibiotics (chloramphenicol and metronidazole), immunosuppressants (cyclophosphamide, cyclosporin A, cyclosporin E, and azathioprine), chemotherapeutic drugs (melphalan, tamoxifen, lomustine, teniposide, and doxorubicin), hormonal drugs (medroxyprogesterone and norethindrone), and anticonvulsants (phenobarbital, phenytoin). Though most of these drugs have been previously assessed under the *Food and Drug Act* for their safety of use, the potential impact that they could have on the environment and human health (as a result of production and disposal) was not assessed; hence their consideration under the CMP.

Using the screening assessment, the Government of Canada examined these PhACs to address their presence in source waters as a result of a point source or down-the-drain discharge. The screening assessment is the most basic form of risk assessment that is carried out to determine if a chemical substance is potentially toxic to the environment and human health, according to section 64 of *CEPA*. Section 64 of *CEPA* defines a substance as toxic "if it is entering or may enter the environment in a quantity or concentration or under conditions that (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity; (b)constitute or may constitute a danger to the environment on which life depends, or (c) constitute or may constitute danger to human life or health in Canada". Following a screening assessment, three results can emerge: (i) no further action is required to be taken concerning the chemical substance, (ii) the chemical substance is toxic and measures are needed for control, or (iii) the chemical substance is placed on the Priority Substance List (PSL).

After the screening assessment, it was concluded that 23 out of the 28 PhACs are not expected to remain in the environment for a long time or accumulate in organisms. While five were indicated to have the potential to remain in the environment for a long time, they are not expected to bioaccumulate in organisms. Notably, these PhACs are also expected to be discharged into the environment below concentrations that could cause harm to organisms or constitute danger to the environment. The assessment

concluded that no further action was needed to be taken on any of the 28 PhACs, thereby, clearing them all that they are not toxic according to the criteria highlighted under section 64 of *CEPA*.

The findings from this assessment prompt important questions: did the screening assessment take into account PhACs that are commonly reported in the environment? how about the PhACs that have been commonly reported in scientific literature to be deleterious to the aquatic environment (Kidd et al., 2007; Metcalfe et al., 2010; Du et al., 2015; Vernouillet et al., 2010)? What were the criteria used for selecting the PhACs that were analyzed? Did the screening consider lab-based experiments or use models alone to make predictions about the toxicity of the PhACs to the environment? Did the screening also consider the synergistic effects of PhACs? There is a need to ascertain that the findings from scientific literature agree with the conclusions of the CMP. The CMP has played a vital role in screening most of the PhACs in the Canadian environment and that is worthy of recognition. However, because it represents one of the major lines of defense that Canada has against the presence and impacts of contaminants like PhACs, there is a need to ensure that its decisions fully corroborate with the decisions of science on that subject. For example, because the screening assessment covers a wide range of different categories of drugs, it is possible to think that other drugs that belong to those categories that were not assessed will also react the same way, having no impact on aquatic health like the 28 PhACs. But Knacker & Metcalfe, (2010) noted that PhACs belonging to the same group may incite different ecotoxicological responses in test organisms. This shows why the screening assessment shouldn't stop with 28 PhACs considering that there are several PhACs in the environment, more screening assessments should be done and methods adopted in scientific literature should be employed. Based on this, PhACs that enter the environment must be properly monitored, screened, and managed using treatment options that are known to be effective and will reduce the rate at which they end up in source waters or eliminate them.

The Management of PhACs in other Countries

Monitoring of PhACs

Some Member States in the European Union (EU) have taken the necessary steps in the right direction to protect the environment just like Canada. But unlike Canada, some of these countries appear to have a more coordinated approach and strategic approach to achieving that. For example, the EU has a more coordinated monitoring and surveillance program. The Water Framework Directive 2000/60/EC was adopted in 2000 by the EU as a legislative tool that establishes a protection regime for all waters including groundwater, surface water, transitional waters, and coastal waters. Part of the objectives of the directive is to progressively reduce the emission of hazardous substances in water. In doing that, a Priority Substances Directive was created to protect the water sources against pollution by PhACs. Though PhACs have not been added to the list yet, some PhACs are currently being monitored as the EU has created a watch list of substances that are currently being monitored and some PhACs are on the list. The list was updated in 2020 to accommodate more PhACs. These PhACs include erythromycin, diclofenac, 17 alpha-ethinylestradiol, clarithromycin, 17 beta-estradiol, azithromycin, amoxicillin, and ciprofloxacin, sulfamethoxazole, trimethoprim, venlafaxine, O-desmethylvenlafaxine, clotrimazole, fluconazole, and miconazole. This list mostly contains PhACs belonging to the category of hormonal drugs and antibiotics and it is noteworthy that these are more commonly reported in the environment by scientific literature than the PhACs screened by the CMP. These have been added to their watchlist while Canada has no watchlist for PhACs.

Regulatory Limits and Advanced Treatment Options

Since conventional treatment processes do not remove PhACs from wastewater as earlier discussed, some countries are implementing regulations that will eliminate microcontaminants like PhACs from their wastewater. For example, Switzerland has put a regulation in place that will limit the rate at which PhACs will end up in source waters by upgrading their WWTPs to remove microcontaminants. This regulation undertakes a 20-year plan to upgrade about 100 of the country's urban WWTPs to incorporate advanced treatment within 20 years (Aqua Strategy, 2016). This advanced treatment is aimed to achieve an overall

reduction of 80% in the micropollutants that are released from the treatment plants. One of these advanced treatment options will employ ozonation which is known to be very effective in removing PhACs, pesticides, and some industrial chemicals (Aqua Strategy, 2016). California also has a regulation in place that ensures that before recycled water is used to recharge groundwater, they are monitored for priority contaminants which include some PhACs such as triclosan, 17β-estradiol, iopromide, and gemfibrozil (Pollution Probe, 2019).

Regarding the effluents from pharmaceutical industries and healthcare facilities, while there is no specific legislation at the EU level, some Member States have implemented discharge limits to reduce the rate at which PhACs are present in their wastewater. For example, Denmark has put in place the maximum concentrations for 40 PhACs that are allowed before wastewater effluents are discharged into the sewers (Pollution Probe, 2019).

Comparing Canada with other countries reveals the significant steps that are being taken to address this problem and the precautionary measures that other countries are taking despite that the science around the impacts of PhACs is not entirely clear. Sweden is a good example of that, banning the use of antibiotics in animals as early as 1986, as concerns over their use as growth promoters began to increase in the 1990s. This was before they became a Member State in the EU in 1995, even before there was clear scientific proof of harm (Holtz, 2006). Regulations were not implemented to ban antibiotics as growth promoters until 2006 in the EU.

The progress made in the EU concerning the management of PhACs is not to undermine the significant measures that Canada has put in place and is also currently undertaking to protect the environment. For example, in Canada, the medication return program (MRP) has been very successful in Ontario, British Columbia, and some other provinces. The MRPs are operated by the Health Products Stewardship Association (HPSA), which is the industry funding organization that represents producers of consumer health products in Canada. They ensure the safe disposal of drugs and divert them from being improperly discharged into the environment. For example, in Ontario, as of December 2020, their active collection points were 4,146, with a 91.2% participation rate by eligible collection locations, retrieving about 287, 360 kg of PhACs (HPSA, 2020). This program has been beneficial because, not only does it shift the financial responsibility of collecting and disposing of these drugs from taxpayers and the government to the manufacturers (Kingsmore, 2013), but it also ensures that fewer PhACs make it into the environment. This program is currently effective and needs to be further strengthened to ensure that more PhACs are collected and disposed of safely.

Conclusions and Recommendations

The amount of PhACs that are released into the environment has been on a continuous increase annually, and so has the population of Canadians. A continuous increase in population leads to an increase in drug production and consumption, which in turn, increases the concentration of drugs that eventually reach the environment from different sources. Addressing the impacts that these PhACs have on the environment and how they are being currently managed in Canada has revealed some gaps. Notably, there are lessons to learn from how other countries are managing the presence of PhACs in their environment. The EU, for example, has had some management measures in place for about 20 years, meaning time has afforded them the privilege of putting more stringent measures in place than Canada. Another reason might simply be due to the increasing and valid concerns that the EU has regarding the scarcity of water resources, as water demand is on a continual increase, unlike Canada where there is an abundant supply of freshwaters, it might be difficult to see the urgency of the issue. In the EU, a significant percentage of the population deals with water scarcity, totaling about 100 million people. Since about 88% of freshwater usage in Europe comes from rivers and groundwater while 1.5% and 10.3% come from lakes and reservoirs, respectively (European Environmental Agency, 2018), this could attest to why there are more stringent regulations on water protection from CECs like PhACs.

Canada doesn't need to wait for absolute certainty before putting more stringent measures in place to protect the aquatic environment against CECs because waiting might be hazardous to the future of environmental health. Most of the progress recorded in the EU could be attributed to how the precautionary principle is woven into their core environmental codes and regulations. According to Article 191, which is the consolidated version of the treaty on the functioning of the EU, "Union policy shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay". The wording of this rule attests to the emphasis that the EU places on preventive measures and source control of environmental pollutants. Considering that it is going to be more financially difficult to upgrade treatment solutions at the WWTP (since taxpayers are responsible for municipal treatment plants), the Canadian government needs to emulate the EU approach and put management options at the source. In light of this, a few recommendations could be of great benefit:

Recommendation 1) Municipal governments should monitor and regulate effluent discharge by prohibiting PhAC industries from discharging wastes directly into municipal water systems and sewers. This will ensure that they treat their waste before releasing it. While this is technically possible, it may be difficult to implement this immediately across all municipalities due to the heavy economic burden that it puts on municipalities and industries in terms of costs. Therefore, the provincial government can start by working with municipalities with PhAC industries that discard directly into urban WWTPs. Instead of upgrading WWTPs themselves, which is a more politically difficult option due to the burden that it puts on taxpayers, source control is a more feasible option as it regulates polluters by setting up regulatory discharge limits at the source and requires polluters to take responsibility for their pollution.

Recommendation 2) The CMP screen more PhACs than those 28 previously screened in 2015. The screening should include PhACs that are more frequently reported in the environment by researchers. It should also consider the synergistic effects of PhACs and adopt methods that have been used in the scientific literature in studying PhACs. Adopting this approach will bring some form of conformity and veracity to evidence from science and under the CMP initiative about the true risk of PhACs to the aquatic environment.

Recommendation 3) The federal government should provide more funding for interdisciplinary research that will study the impact and management of PhACs from a holistic approach. Interdisciplinary synergies between science, engineering, and public policy studies can help shed light on areas overlooked by policymakers.

References

Agunbiade, F. O., & Moodley, B. (2014). Pharmaceuticals as emerging organic contaminants in Umgeni River water system, KwaZulu-Natal, South Africa. *Environmental Monitoring and Assessment*. https://doi.org/10.1007/s10661-014-3926-z

Alcock, R. E., Sweetman, A., & Jones, K. C. (1999). Assessment of organic contaminant fate in waste water treatment plants. I: Selected compounds and physicochemical properties. *Chemosphere*. https://doi.org/10.1016/S0045-6535(98)00444-5

Anderson, M., Clift, C., Schulze, K., Sagan, A., Nahrgang, S., Ait Ouakrim, D., & Mossialos, E. (2019). Averting the AMR crisis: What are the avenues for policy action for countries in Europe? In *European Observatory Policy Briefs*.

Angeles, L. F., Mullen, R. A., Huang, I. J., Wilson, C., Khunjar, W., Sirotkin, H. I., McElroy, A. E., & Aga, D. S. (2020). Assessing pharmaceutical removal and reduction in toxicity provided by advanced wastewater treatment systems. *Environmental Science: Water Research and Technology*. https://doi.org/10.1039/c9ew00559e

Archer, E., Petrie, B., Kasprzyk-Hordern, B., & Wolfaardt, G. M. (2017). The fate of pharmaceuticals and personal care products (PPCPs), endocrine disrupting contaminants (EDCs), metabolites and illicit drugs in a WWTW and environmental waters. *Chemosphere*. https://doi.org/10.1016/j.chemosphere.2017.01.101

Archer, E., Wolfaardt, G. M., & van Wyk, J. H. (2017). Pharmaceutical and personal care products (PPCPs) as endocrine disrupting contaminants (EDCs) in South African surface waters. In *Water SA*. https://doi.org/10.4314/wsa.v43i4.16

Barnes, K. K., Christenson, S. C., Kolpin, D. W., Focazio, M. J., Furlong, E. T., Zaugg, S. D., Meyer, M. T., & Barber, L. B. (2004). Pharmaceuticals and other organic waste water contaminants within a leachate plume downgradient of a municipal landfill. In *Ground Water Monitoring and Remediation*. https://doi.org/10.1111/j.1745-6592.2004.tb00720.x

Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., & Snyder, S. A. (2009). Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. *Environmental Science and Technology*. https://doi.org/10.1021/es801845a

Blair, B. D., Crago, J. P., Hedman, C. J., & Klaper, R. D. (2013). Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern. *Chemosphere*. https://doi.org/10.1016/j.chemosphere.2013.07.057

Bound, J. P., Kitsou, K., & Voulvoulis, N. (2006). Household disposal of pharmaceuticals and perception of risk to the environment. *Environmental Toxicology and Pharmacology*. https://doi.org/10.1016/j.etap.2005.09.006

Daughton, C. G. (2009). Chemicals from the practice of healthcare: Challenges and unknowns posed by residues in the environment. In *Environmental Toxicology and Chemistry*. https://doi.org/10.1897/09-138.1

Daughton, C. G., & Ternes, T. A. (1999). Pharmaceuticals and personal care products in the environment: Agents of subtle change? In *Environmental Health Perspectives*. https://doi.org/10.1289/ehp.99107s6907

Du, B., Haddad, S. P., Scott, W. C., Chambliss, C. K., & Brooks, B. W. (2015). Pharmaceutical bioaccumulation by periphyton and snails in an effluent-dependent stream during an extreme drought. *Chemosphere*. https://doi.org/10.1016/j.chemosphere.2014.08.044

Ebele, A. J., Abou-Elwafa Abdallah, M., & Harrad, S. (2017). Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. In *Emerging Contaminants*. https://doi.org/10.1016/j.emcon.2016.12.004

Edwards, M., Topp, E., Metcalfe, C. D., Li, H., Gottschall, N., Bolton, P., Curnoe, W., Payne, M., Beck, A., Kleywegt, S., & Lapen, D. R. (2009). Pharmaceutical and personal care products in tile drainage following

surface spreading and injection of dewatered municipal biosolids to an agricultural field. *Science of the Total Environment*. https://doi.org/10.1016/j.scitotenv.2009.02.028

Galus, M., Jeyaranjaan, J., Smith, E., Li, H., Metcalfe, C., & Wilson, J. Y. (2013). Chronic effects of exposure to a pharmaceutical mixture and municipal wastewater in zebrafish. *Aquatic Toxicology*. https://doi.org/10.1016/j.aquatox.2012.12.016

Hicks, K. A., Fuzzen, M. L. M., McCann, E. K., Arlos, M. J., Bragg, L. M., Kleywegt, S., Tetreault, G. R., McMaster, M. E., & Servos, M. R. (2017). Reduction of Intersex in a Wild Fish Population in Response to Major Municipal Wastewater Treatment Plant Upgrades. *Environmental Science and Technology*. https://doi.org/10.1021/acs.est.6b05370

Hignite, C., & Azarnoff, D. L. (1977). Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. *Life Sciences*. https://doi.org/10.1016/0024-3205(77)90329-0

Islam, G. M., & Gilbride, K. A. (2019). The effect of tetracycline on the structure of the bacterial community in a wastewater treatment system and its effects on nitrogen removal. *Journal of Hazardous Materials*. https://doi.org/10.1016/j.jhazmat.2019.02.032

Johnson, A. C., & Sumpter, J. P. (2016). Are we going about chemical risk assessment for the aquatic environment the wrong way? *Environmental Toxicology and Chemistry*. https://doi.org/10.1002/etc.3441

Kidd, K. A., Blanchfield, P. J., Mills, K. H., Palace, V. P., Evans, R. E., Lazorchak, J. M., & Flick, R. W. (2007). Collapse of a fish population after exposure to a synthetic estrogen. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0609568104

Kleywegt, S., Payne, M., Ng, F., & Fletcher, T. (2019). Environmental loadings of Active Pharmaceutical Ingredients from manufacturing facilities in Canada. *Science of the Total Environment*. https://doi.org/10.1016/j.scitotenv.2018.07.240

Kleywegt, S., Pileggi, V., Yang, P., Hao, C., Zhao, X., Rocks, C., Thach, S., Cheung, P., & Whitehead, B. (2011). Pharmaceuticals, hormones and bisphenol A in untreated source and finished drinking water in Ontario, Canada - Occurrence and treatment efficiency. *Science of the Total Environment*. https://doi.org/10.1016/j.scitotenv.2011.01.010

Knacker, T., & Metcalfe, C. (2010). Introduction to the special issue on environmental risk assessment of pharmaceuticals. In *Integrated Environmental Assessment and Management*. https://doi.org/10.1002/ieam.93

Kołecka, K., Gajewska, M., Stepnowski, P., & Caban, M. (2019). Spatial distribution of pharmaceuticals in conventional wastewater treatment plant with Sludge Treatment Reed Beds technology. *Science of the Total Environment*. https://doi.org/10.1016/j.scitotenv.2018.07.439

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. *Environmental Science and Technology*. https://doi.org/10.1021/es011055j

Kriebel, D., Tickner, J., Epstein, P., Lemons, J., Levins, R., Loechler, E. L., Quinn, M., Rudel, R., Schettler, T., & Stoto, M. (2001). The precautionary principle in environmental science. *Environmental Health Perspectives*. https://doi.org/10.1289/ehp.01109871

Kümmerer, K. (2001). Drugs in the environment: Emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources - A review. *Chemosphere*. https://doi.org/10.1016/S0045-6535(01)00144-8

Lagesson, A., Fahlman, J., Brodin, T., Fick, J., Jonsson, M., Byström, P., & Klaminder, J. (2016). Bioaccumulation of five pharmaceuticals at multiple trophic levels in an aquatic food web - Insights from a field experiment. *Science of the Total Environment*. https://doi.org/10.1016/j.scitotenv.2016.05.206

Loos, R., Carvalho, R., António, D. C., Comero, S., Locoro, G., Tavazzi, S., Paracchini, B., Ghiani, M., Lettieri, T.,

Blaha, L., Jarosova, B., Voorspoels, S., Servaes, K., Haglund, P., Fick, J., Lindberg, R. H., Schwesig, D., & Gawlik, B. M. (2013). EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. *Water Research*. https://doi.org/10.1016/j.watres.2013.08.024

Metcalfe, C. D., Chu, S., Judt, C., Li, H., Oakes, K. D., Servos, M. R., & Andrews, D. M. (2010). Antidepressants and their metabolites in municipal wastewater, and downstream exposure in an urban watershed. *Environmental Toxicology and Chemistry*. https://doi.org/10.1002/etc.27

Metcalfe, C. D., Metcalfe, T. L., Kiparissis, Y., Koenig, B. G., Khan, C., Hughes, R. J., Croley, T. R., March, R. E., & Potter, T. (2001). Estrogenic potency of chemicals detected in sewage treatment plant effluents as determined by in vivo assays with Japanese medaka (Oryzias latipes). *Environmental Toxicology and Chemistry*. https://doi.org/10.1002/etc.5620200210

Metcalfe, C., Miao, X.-S., Hua, W., Letcher, R., & Servos, M. (2004). Pharmaceuticals in the Canadian Environment. In *Pharmaceuticals in the Environment*. https://doi.org/10.1007/978-3-662-09259-0_6

Petrie, B., Barden, R., & Kasprzyk-Hordern, B. (2015). A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring. *Water Research*. https://doi.org/10.1016/j.watres.2014.08.053

Richardson, M. L., & Bowron, J. M. (1985). The fate of pharmaceutical chemicals in the aquatic environment. In *Journal of Pharmacy and Pharmacology*. https://doi.org/10.1111/j.2042-7158.1985.tb04922.x

Sacher, F., Lange, F. T., Brauch, H. J., & Blankenhorn, I. (2001). Pharmaceuticals in groundwaters: Analytical methods and results of a monitoring program in Baden-Württemberg, Germany. *Journal of Chromatography A*. https://doi.org/10.1016/S0021-9673(01)01266-3

Snyder, S. A. (2008). Occurrence, treatment, and toxicological relevance of EDCs and pharmaceuticals in water. *Ozone: Science and Engineering*. https://doi.org/10.1080/01919510701799278

Sumpter, J. P., & Harris, C. A. (2016). In Response: An academic perspective. In *Environmental Toxicology and Chemistry*. https://doi.org/10.1002/etc.3195

Tehrani, A. H., & Gilbride, K. A. (2018). A closer look at the antibiotic-resistant bacterial community found in urban wastewater treatment systems. *MicrobiologyOpen*. https://doi.org/10.1002/mbo3.589

Vernouillet, G., Eullaffroy, P., Lajeunesse, A., Blaise, C., Gagné, F., & Juneau, P. (2010). Toxic effects and bioaccumulation of carbamazepine evaluated by biomarkers measured in organisms of different trophic levels. *Chemosphere*. https://doi.org/10.1016/j.chemosphere.2010.05.010

Williams, M., Backhaus, T., Bowe, C., Choi, K., Connors, K., Hickmann, S., Hunter, W., Kookana, R., Marfil-Vega, R., & Verslycke, T. (2016). Pharmaceuticals in the environment: An introduction to the ET&C special issue. In *Environmental Toxicology and Chemistry*. https://doi.org/10.1002/etc.3394