AN EVALUATION OF BRITISH COLUMBIA'S MEDICATIONS RETURN PROGRAM AS A MANAGEMENT FRAMEWORK FOR COLLECTING UNUSED/EXPIRED PHARMACEUTICALS

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ABSTRACT

An Evaluation of British Columbia's Medication Return Program as a Management Framework for Collecting Unused/Expired Pharmaceuticals

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This thesis examines British Columbia's Medications Return Program, which is a management framework for collecting and disposing of leftover residential drugs. British Columbia's Medications Return program is evaluated against the Canadian Council of Ministers of the Environment (CCME) principles for an effective Extended Producer Responsibility program. A medication take-back program has limitations as an environmental management framework. The management approach captures only the amounts that are potentially discarded, while medications that are used and metabolized remain an aquatic system problem.

Scientific evidence on the potential effects of pharmaceutical residues to aquatic organisms as well as the key regulations on managing the risks is highlighted. The Canadian government has committed to using the precautionary principle when there is a lack of full scientific certainty.

The results achieved indicate that despite the Medications Return Program being successful from a process perspective, the pharmaceutical industry has not aligned its program with CCME's principle.

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Acronyms

4Rs	Reduce, Reuse, Recycle, Recovery
AMR	Antimicrobial Resistance
CCME	Canadian Council of Ministers of the Environment
CEPA	Canadian Environmental Protection Act
DIY	Do-it-yourselfer
EAR	Environmental Assessment Regulation
EE_2	Ethinylestradiol
EDS	Endocrine Disrupting Substance
EPA	Environmental Protection Agency
EPR	Extended Producer Responsibility
GSI	Gonadosomatic Indices
ICH	International Conference of Harmonisation of Pharmaceuticals for Human Use
LOEC	Lowest Observed Effects Concentration
mRNA	Messenger Ribonucleic Acid
NEPA	National Environmental Policy Act
NSNR	New Substances Notification Regulation
NOEC	No Observed Effects Concentration
OECD	Organisation for Economic Co-operation and Development
PhAC	Pharmaceutically Active Compound
PPCP	Pharmaceuticals and Personal Care Products
PCPSA	Post-Consumer Pharmaceuticals Stewardship Association
RxA	Alberta Pharmacists' Association
VTG	Vitellogenin

1. Introduction

Leftover household medications have the potential to be widespread environmental contaminants when improperly disposed. The terms "medications," "pharmaceuticals" and "drugs" are used interchangeably throughout this document. The Teleosis Institute in California collected data on unused drugs from July 1 to December 31, 2007, and reported that of the prescription drugs collected, consumers did not use nearly 45 percent of what they were prescribed (Siler et al., 2008; 8). As evidenced by a number of studies, the most common disposal methods of leftover household medications (e.g. prescription drugs and non-prescription drugs) include flushing down the toilet or sink, or disposing in the trash. Since wastewater treatment plants are not designed to treat all medicinal substances, these chemicals pass through the system either changed or unchanged, and are released into the surrounding environment. Similarly, disposal of leftover medication to the trash will end up in the landfills and theoretically leach into groundwater and enter the drinking water supply.

The primary concern regarding pharmaceutical compounds in the water system is their potential effects on non-target aquatic organisms. While the concentration levels of these chemicals in the environment are low combined with low toxicity, there is growing evidence that certain compounds may pose potentially significant and non-reversible effects. Research continues to demonstrate that synthetic steroid estrogens have disrupted reproductive endocrine functions in wildlife, particularly fish inhabiting waters that receive untreated municipal effluents from wastewater treatment plants (Kidd et al., 2007; 8897). Many of these compounds are persistently present in the environment given that they are constantly replenished. In light of mounting scientific evidence and increasing public pressure to take action to reduce the potential risk of pharmaceutical compounds, the Canadian federal government has adopted regulations to increase oversight of the situation. Manufacturers or importers of new substances, which include pharmaceutically active ingredients, are required to assess the potential risks they may pose to the environment or human health. British Columbia is one of the few provinces that have specific regulations pertaining to pharmaceutical collection and disposal in an

effort to reduce the potentially negative effects on the environment from flushing or disposing of drugs in landfills.

1.1 Study Objective and Scope

The main purpose of the study that follows is to examine the usefulness and effectiveness of British Columbia's Medications Return Program as an environmental management framework for collecting and disposing of leftover residential drugs and thereby reducing the overall loadings to the environment. In order to determine this, British Columbia's Medication Return Program will be assessed and evaluated against: 1) Results achieved from different take-back programs from four other jurisdictions, and 2) Canadian Council of Ministers of the Environment's (CCME) principles for an effective Extended Producer Responsibility (EPR) program/policy.

To better understand the issues related to improper disposal of leftover drugs, this study begins by exploring the nature of Canada's pharmaceutical market. It will be followed by a review of the literature on the sources, occurrences and potential effects of pharmaceuticals and personal care products in the Canadian aquatic environment, which include wastewater treatment plant effluents, surface waters, drinking water and biota. The second part of this study looks at the regulatory landscape in Canada, including federal, provincial and municipal initiatives, with respect to managing the risks of pharmaceuticals as environmental contaminants. Relevant policies in the United States and Europe pertaining to pharmaceutical management in the environment will be reviewed. Lastly, a possible management framework, British Columbia's Medications Return Program will be assessed and evaluated in greater detail to determine whether it has been an effective and sensible drug disposal strategy, and will be the focus of this study.

1.2 Study Limitations

The scope of this study was limited. The data sources used for evaluating British Columbia's Medications Return Program included primarily annual reports, published documents and written inquiries to the stewardship organization. There are gaps in the

available data that arise because the stewardship organizations, in some cases, consider the information on their activities as proprietary.

In addition, examination of the different take-back programs from the four other jurisdictions was not an exhaustive study. The focus was on the policy tools used to implement the programs and the results achieved.

1.3 Key Assumptions

1) Medication take-back programs has limitations as an environmental management framework since it captures only the amounts that are potentially discarded while medications that are used and metabolized remain an aquatic system problem.

2) Regulation and enforcement can improve the capture of medications only to a certain extent; additional contaminant removal requires corporate and personal responsibility.

3) Studies have shown that while there are no clear and immediate human health risks, there are potential for aquatic effects, particularly on reproduction. Based on existing evidence, there is enough concern to raise the question of environmental management of pharmaceuticals and personal care products.

2. Canada's Pharmaceutical Market

Canada is one of the world's leading pharmaceutical markets. According to IMS Canada, Canadian pharmacists dispensed 453 million prescriptions in 2008, an average of nearly 14 prescriptions per Canadian; in Ontario alone, the retail spending per capita annually is $646, an average of 11 prescriptions per Ontarian. IMS Canada reports that prescriptions filled by Canadians grew 7.1 percent in 2008 and in the same year, they spent $21.4 billion on prescription medications, which is up from $20.2 billion in 2007 (IMS Canada, November 2009). Health Canada's Drug Products Database lists all the drug products marketed in Canada. Those database product listings have increased from about 17,000 in 1987 to over 24,000 in 2004, of which more than 2,500 are approved veterinary products (Holtz, 2006; 8). The data indicate that the top five categories of drugs based on total prescriptions include cardiovascular, psychotherapeutic, gastrointestinal, cholesterol agents and hormones (IMS Canada,

November 2009). In addition, non-prescription drugs are sold in even higher quantities than prescription drugs. These figures reflect a growing trend of purchase and usage.

Based on these findings, it is clear that the use and consumption of drugs has amplified in the past several decades. This is largely attributed to the constant introduction of new products in the marketplace, expanding uses for existing drugs (e.g., "chemopreventatives" used to reduce the chances of disease or slow its onset), the growing practices of off-label prescribing (this refers to drug use directed at conditions for which the relevant regulatory authority have not deemed the drug dose effective), and abusing prescription drugs for non-medical, recreational purposes (Daughton, 2001; 11). Furthermore, veterinary medicine and agricultural pharmaceuticals are playing a greater role in disease prevention and treatment, and as growth promoters.

3. Background on Pharmaceuticals and Personal Care Products in the Environment

Pharmaceuticals and personal care products have been present in the aquatic environment as long as drugs and consumer products have been available. However, pharmaceuticals and personal care products, which will be simplified to PPCPs from this point, received little attention as environmental pollutants until reports surfaced of pharmaceutically active compounds (PhACs) being detected in Canadian wastewater effluents, surface water, and drinking water. There was a groundbreaking study conducted in the mid-1980s in Vancouver, British Columbia, where trace concentrations of two analgesic/anti-inflammatory drugs, ibuprofen and naproxen, were identified in the municipal wastewater. Since this study, a larger picture of the issue has been emerging. To date, more than 30 pharmaceuticals and their metabolites have been detected in the Canadian aquatic environment (Metcalfe et al., 2004; 86). Further to this, the advances in analytical instruments, particularly the liquid chromatographs combined with mass spectrometry, has made it possible to identify polar organic pollutants, including pharmaceuticals, at low levels in various liquid media and solid matrices (Marsalek, 2008; 117).

PPCPs are a diverse and complex group of chemicals with properties that raise suspicions about environmental effects. PhACs are molecules with different functionalities, physicochemical and biological properties. Many pharmaceuticals undergo biotransformation including biodegradation, which modifies the chemical structure of their active molecules, which in turn often results in a change in their physicochemical and pharmaceutical properties (Kummerer, 2004; 3). The category PPCPs comprises all drugs, diagnostic agents (e.g., X-ray contrast media), "nutraceuticals" (bioactive food supplements such as huperzine A), and other consumer chemicals, such as fragrances (e.g., musks), sun-screen agents (e.g., methylbenzylidene camphor), and skin anti-aging preparations (e.g., retinoids) (Daughton 2001; 9). Many PPCPs are bioactive compounds and inadvertently enter the aquatic environment as complicated mixtures. They differ from agro-chemicals in that they often have multiple functional groups (including ionizable groups and more frequent and extensive fluorination); drug structures also span the spectrum from very simple low-molecular weight structures to large, complex molecules; most drugs are neither bioaccumulative nor volatile; and personal care products, such as the musk fragrances and sun-screen agents, tend to be lipophilic (Daughton, 2001; 9). Despite these distinctions, much of the existing research groups together PPCPs, along with various industrial and other chemicals that are suspected endocrine-disrupting substances (EDSs) (Holtz, 2006; 5). In fact, only a small subset of PPCPs is known to be EDS(s).

There are number of PPCP classes (and individual members) that have been commonly surveyed in various environmental samples (Table I).

Therapeutic class	Example Generic Name	Example Brand Name
analgesics/non-steroidal anti-inflammatories (NSAIDs)	acetaminophen (analgesic)	Tylenol
	diclofenac	Voltaren

	ibuprofen ketoprofen naproxen	Advil Oruvail Naprosyn
antimicrobials	e.g., sulfonamides, fluoroquinolones	Many
Antiepileptics	carbamazepine	Tegretal
antihypertensives (betablockers, beta-adrenergic receptor inhibitors)	bisoprolol metoprolol	Concor Lopressor
antineoplastics	cyclophosphamide ifosfamide	Cycloblastin Holoxan
antiseptics	triclosan	Igrasan DP 300
contraceptives	-estradiol 17-ethinyl estradiol	Diogyn Oradiol
$_2$-sympathomimetics (bronchodilators)	albuterol	Ventolin
lipid regulators (anti-lipidemics; cholesterol-reducing agents; and their bioactive metabolites)	clofibrate (active metabolite: clofibric acid) gemfibrozil	Atromid-S Lopoid

musks (synthetic)	nitromusks polycyclic musks reduced metabolites of nitromusks	musk xylene Celestolide substituted amino nitrobenzenes
anti-anxiety/hypnotic agents	diazepam	Valium
sun screen agents	methybenzylidene camphor avobenzene octyl methoxycinnamate	Eusolex 6300 Parsol A Parsol MOX
X-ray contrast agents	diatrizoate	Hypaque

Table I. Representative classes (and members) of PPCPs reported in wastewater treatment plants and environmental samples (Source: Daugton, 2001)

Alternatively, there are classes of drugs that have yet to be subjected to environmental surveys (Table II).

Therapeutic class	Example generic name (many drugs cross over into multiple classes)	Example brand name
adrenergic receptor inhibitors (anti-BPH agents)	terazozin, doxazosin, finasteride	Hytrin, Cardura, Proscar/Propecia
amyotrophic lateral sclerosis	riluzole	Rilutek
analgesics (non-NSAIDs and narcotics)	tramadol, propoxyphene, oxycodone, hydrocodone	Darvon, Ultram, Tylox
anorexiants (diet drugs)	fenfluramine, orlistat	Pondimin, Xenical
antiarrhythmics	disopyramide, flecainide,	Norpace

	amiodarone, sotalol	
anticoagulants	warfarin	Coumadin
antidepressants	esp. SSRIs (sertraline, paroxetine, fluoxetine, fluvoxamine), tricyclics (desipramine), MAOIs (phenelzine)	Zoloft, Paxil, Prozac, Luvox, Wellbutrin (bupropion), Serzone (nefazadone), Effexor (venlafaxine)
antidiabetic agents	insulin sensitizers, antihyperglycemic (e.g., sulfonyluereas)	Rezulin (troglitazone), Glucophage (metformin), Glucotrol (glipizide), Diaeta (glyburide)
antihistamines (H-1 blockers)	fexofenadine, loratadine, cetirizine, terfenadine	Allegra, Claritin, Zyrtec, Seldane
histamine (H-2) blockers	famotidine, ranitidine, nizatidine	Pepcid, Zantac, Axid
decongestants	ephedrines	
anti-infectives	many special disease classes (amebicides, anti-fungals, -malarials, -tuberculosis, -leprosy, -viral) and chemical classes	Diflucan (fluconazole)
antimetabolites	methotrexate	Rheumatrex
antipsychotics, CNS agents	alprazolam, zolpidem, clonazepam, risperidone, temazepam thioridazine, trifluoperazine	Xanax, Ambien, Klonopin, Risperdal, Restoril
calcium-channel blockers	diltiazem, nifedipine, amlodipine, verapamil	Cardizem, Procardia, Norvasc
digitalis analogs	digoxin, digitoxin	Lanoxin
diuretics	thiazide (hydrochlorothiazide, chlorthalidone); loop (furosemide, bumetanide); potassium-sparing (spironolactone, triamterene)	Lasix (furosemide) Dyazide (hydrochlorothiazide, triamterene)
dopamine agonists	anti-Parkinsonian agents (e.g., pramipexole, ropinirole)	Mirapex, Requip

Expectorants	guaifenesin	Entex
gastrointestinal agents (ulcer drugs)	omeprazole, lansoprazole, cimetidine	Prilosec, Prevacid, Tagamet
HIV drugs	protease inhibitors, anti-retrovirals (nucleoside analogs/reverse transcriptase inhibitors)	Crixivan (indinavir), Retrovir (zidovudine)
hormonally active agents		Accutane, Retin-A
androgens	fluoxymesterone	Flovent
anti-acne agents	isotretinoin, tretinoin	Nolvadex
adrenocortico steroids	prednisone, triamcinolone	
inhalable steroids	fluticasone	
estrogen antagonists	tamoxifen	
muscle relaxants	cyclobenzaprine	Flexeril
osteoporosis agents (biphosphonates)	alendronate sodium	Fosamax
prostaglandin agonists	latanoprost	Xalatan
psychostimulants (amphetaminelike)	methylphenidate, dextroamphetamine	Ritalin
Retinoids	tretinoin	Retin-A; Vesanoid
sexual function agents	sildenafil citrate	Viagra
vasodilators (esp. angiotensin converting enzyme [ACE] inhibitors)	lisinopril, enalapril, quinapril, benazepril	Zestril, Vasotec, Accupril,
	losartan, fosinopril, ramipril	Lotensin
		Cozaar, Monopril

street drugs (illicit, illegal, recreational)	many: e.g., see http://www.streetdrugs.org/; National Institute of Drug Abuse (NIDA): http://www.nida.nih.gov/NIDAHome1.htm
newly approved, upcoming, and investigational drugs	ongoing; see listing at: "LexiComp.org" (http://www.lexi.com/web/newdrugs.jsp)
"chemosensitizers", efflux pump inhibitors (EPIs)	verapamil (and others from diverse classes; e.g., see: http://www.microcide.com/ICAAC99Posters/ icaac99_posters.html) [post-publication note -- Corporate name changed. See new information at: http://www.essentialtherapeutics. com/rnd_pubs.html; http://www.essentialtherapeutics. com/prod_pipeline.html
cytochrome P450 inhibitors/inducers	http://medicine.iupui.edu/flockhart/

Table II. Representative distinct classes of drugs for which concerted environmental surveys have not been performed (Source: Daugton, 2001)

3.1 Sources

The sources of PPCPs are widespread including point and non-point sources. The primary introduction of PPCPs and their metabolites to the aquatic environment is via treated and untreated sewage effluent discharged from wastewater treatment plants. Ingested medications are excreted with urine and faeces into domestic sewage while products (e.g., shampoos, fragrances, etc.) get washed away with wastewater. About 70 percent of excreted compounds are in urine and 30 percent in faeces (Marsalek; 2008; 118). Substances used in the manufacture of pharmaceuticals and other products are discharged with wastewater from the plant. However, spills reaching the storm sewer system are directly released into the receiving waterways prior to any treatment. Municipal/domestic sewage, more so than hospital sewage, is the major source for most drug classes and quantities (Daughton, 2001; 5). The large stationary point source polluters are easily identifiable and their effluents produce the largest concentrations of PPCPs that can be measured. Non-point sources contribute to pollution generally by being carried off the land by storm water runoff. This largely includes runoff of manure

or sewage sludge spread on farm fields, nutrients from livestock, treatment from aquaculture, and faulty septic systems (Holtz, 2006; 13). All these types of pollution are wide-scale and diffuse in nature. In the past, Canada's government had a tendency to focus on large point source polluters, and as a result, there are fewer data available on smaller and non-point sources of pollution.

3.2 Wastewater

When pharmaceuticals and their metabolites are not eliminated during the wastewater treatment process, there is potential for residue to be released in treated effluent into the aquatic environment. The potential for these compounds to be present in sewage effluent not only depends on the rates of metabolism by humans but also the varied capabilities of degradation by wastewater treatment plants. Degradation of drugs varies quite drastically - from ineffective to complete. For instance, certain compounds have been shown to be removed more efficiently by the following treatment techniques such as reducing the sludge loading rate, increasing the hydraulic retention time, employing nitrification and denitrification as well as using ozonation (H. Jones, 0., et al., 2005; 416). There are some pharmaceuticals that are degraded relatively rapidly in wastewater treatment plants, such as acetylsalicylic acid (aspirin), those that have intermediate biodegradability, such as ibuprofen, while there are other drugs that do not appear to be degraded at all, such as the anti-epileptic, carbamazepine and lipid regulators (Trudeau et al., 2005; 477). PPCPs are subject to some attenuation by such processes as adsorption onto sludge, stripping (from the water phase into the gas phase during aeration) and biological transformations (Marsalek; 2008; 119). Most of the biodegradation occurs in the secondary treatment stage when the compound is exposed to large concentrations of micro-organisms (H. Jones, O., et al., 2005; 403).

Removal efficiency is essentially a joint function of the drug's structure and the treatment technology employed. For waste streams, one might expect poor removals for certain antimicrobials and antineoplastics[1] (because of acute toxicity to various microbial

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1 Antineoplastics – acting to prevent, inhibit or halt the development of a neoplasm (a tumor). Found at: www.medterms.com/script/main/art.asp?articlekey=22631

species) and for highly sterically-hindered[2] compounds (e.g., iodinated contrast media); and effectiveness could also be a function of the waste stream's origin (e.g., hospital waste versus domestic waste) (Daughton, 2001; 12). Generally, molecules with long, highly branched side chains are generally less amenable to biodegradation than unbranched compounds with shorter side chains (H. Jones, 0., et al., 2005; 405). There are additional factors and intricacies involved with treatment effectiveness. These include, the time of day (both composition and volume of sewage influent, the latter of which is largely a function of diurnal population activity, precipitation/runoff input, and industrial contributions) and season (treatment efficiency influenced by temperature and nutrient loads/physicochemical conditions, and dilution of effluent as a function of receiving water volume/flow) (Daughton, 2001; 12). In short, it is a complex set of emissions and unpredictable emission sources.

Researchers have found numerous (different) types of drugs in final treated effluents in Canada. Samples were collected from 18 wastewater treatment plants in 14 municipalities, between 1999 to 2002. These samples were analysed for residues of a relatively small number of prescription and non-prescription drugs (Table III).

2 Steric hindrance or steric resistance occurs when the size of groups within a molecule prevents chemical reactions that are observed in related smaller molecules. Found at: www.answers.com/topic/steric-effects

Analyte	Median (μg l^{-1})	Max (μg l^{-1})	Number of samples collected	Number of samples non-detected
Acidic drugs				
Atorvastatin	0.019	0.044	5	1
Bezafibrate	0.052	0.200	48	15
Clofibric acid	0.030	0.076	26	22
Diclofenac	0.359	28.4	26	15
Fenoprofen	0.062	0.759	26	21
Gemfibrozil	0.043	2.174	26	17
Ibuprofen	1.885	24.6	26	7
Indomethacin	0.021	0.378	8	2
Ketoprofen	0.130	0.130	26	25
Lovastatin	0.014	0.014	1	0
Naproxen	0.168	0.855	26	15
Pravastatin	0.059	0.059	1	0
Salicylic acid	3.6	59.6	18	12
Simvastatin	0.001	0.001	1	0
Neutral drugs				
Caffeine	0.022	0.677	7	0
Carbamazepine	0.107	2.30	26	0
CBZ-DiOH	1.151	1.325	2	0
CBZ-EP	0.020	0.052	2	0
CBZ-2OH	0.073	0.132	2	0
CBZ-3OH	0.073	0.101	2	0
CBZ-10OH	0.009	0.032	2	0
Cotinine	0.022	0.058	7	0
Cyclophosphamide	0.005	0.009	25	18
Fluoxetine	0.050	0.142	7	2
Ifosfamide	Nd	Nd	18	18
Norfluoxetine	Nd	Nd	6	6
Phenazone	Nd	Nd	18	18
Pentoxyfylline	0.194	0.60	25	14
Trimethoprim	0.071	0.194	7	0

Table III. Concentrations of acidic and neutral drugs in treated effluent samples collected from Canadian wastewater treatment plants during 1999 – 2000 (ug/L) (Source: Metcalfe et al, 2004)

Analgesic/anti-inflammatory compounds, ibuprofen, fenoprofen, ketoprofen and indomethacin, were often detected in sewage effluents (Metcalfe et al., 2004; 73). Ibuprofen was the most frequently detected anti-inflammatory drug, while naproxen was also often present at ug/L concentrations in sewage effluents. Salicyclic acid (i.e., metabolite of acetylsalicyclic acid) was present in several effluent samples collected from Canadian wastewater treatment plants in 1999; sometimes at very high concentrations (Metcalfe et al., 2004; 73). A variety of cholesterol-lowering drugs from the fibrate class including gemfibrozil, bezafibrate and clofibric acid have been detected at ng/L concentrations in the final effluents. The same study showed that diclofenac, gemfibrozil and carbamazepine were also frequently detected in effluents, while ifosfamide, norfluoxetine and phenazone were not present in any sewage samples. In a more recent study, eight major neutral PhAC (carbamazepine, fluoxetine, norfluoxetine, trimethoprim, pentoxyfylline, caffeine, cotinine, cyclophosphamide) were detected in the effluent of the primary wastewater treatment plant for the City of Windsor, Ontario, over a period from September 2002 to June 2003. All of the analytes except caffeine exhibited relatively similar concentrations from low ng/L to middle ng/L levels over the sampling period, while the concentrations for caffeine were one order of magnitude higher during spring (March to April) (Metcalfe et al., 2004; 75).

Studies also reveal trace concentrations of a range of antibiotics in wastewater treatment plant effluents. In a 2003 study, the occurrences of antibiotics in the final effluents from 8 wastewater treatment plants in 5 Canadian cities were reported. Thirty-one antibiotics from the macrolide, quinolone, quinoxaline dioxide, sulfonamide, and tetracycline classes were investigated (Metcalfe et al., 2003; 76) (Table IV).

Analyte	Median ($\mu g\ l^{-1}$)	Max ($\mu g\ l^{-1}$)	Number of samples collected	Number of samples non-detected
Clarithromycin	0.009	0.079	3	0
Erythromycin-H_2O	0.020	0.034	4	1
Roxithromycin	Nd	Nd	4	4
Ciprofloxacin	0.011	0.015	4	2
Enrofloxacin	Nd	Nd	4	4
Norfloxacin	Nd	Nd	4	4
Ofloxacin	Nd	Nd	4	4
Oxolinic acid	Nd	Nd	4	4
Pipemidic acid	Nd	Nd	4	4
Carbadox	Nd	Nd	4	4
Olaquindox	Nd	Nd	4	4
Sulfacetamide	Nd	Nd	4	4
Sulfachloropyridazine	Nd	Nd	4	4
Sulfadiazine	Nd	Nd	4	4
Sulfadimethoxine	Nd	Nd	4	4
Sulfaguanidine	Nd	Nd	4	4
Sulfamerazine	Nd	Nd	4	4
Sulfamethazine	Nd	Nd	4	4
Sulfamethizole	Nd	Nd	4	4
Sulfamethoxazole	0.008	0.099	4	0
Sulfamethoxypyridazine	Nd	Nd	4	4
Sulfamoxole	Nd	Nd	4	4
Sulfapyridine	0.010	0.022	4	2
Sulfaquinoxaline	Nd	Nd	4	4
Sulfathiazole	Nd	Nd	4	4
Sulfisomidine	Nd	Nd	4	4
Sulfisoxazole	Nd	Nd	4	4
Chlorotetracycline	Nd	Nd	4	4
Doxycycline	Nd	Nd	4	4
Oxytetracycline	Nd	Nd	4	4
Tetracycline	0.016	0.016	4	3

Table IV. Concentrations of antibiotics in the effluents from 8 wastewater treatment plants in 5 Canadian cities in 2003 (ug/L) (Source: Metcalfe et al., 2004)

Ciprofloxacin, clarithromycin, erythromycin-H20, ofloxacin, sulfamethoxazole, sulfapyridine, and tetracycline were frequently detected in the effluents (Miao et al., 2004; 3533). The detection of sulfapyridine in effluents is the first report of this compound in environmental samples. Antibiotics used exclusively for veterinary applications or treatment of livestock were not detected in the final effluents (Miao et al., 2004; 3533). Sulfamethazine, which is used exclusively for veterinary applications, was detected in one wastewater treatment effluent sample (Metcalfe et al., 2004; 76). The concentrations detected in the wastewater treatment effluents did not exceed 1 ug/L, which are levels considered unlikely to affect the growth and survival of aquatic organisms (Miao et al., 2004; 3533). However, studies such as this one, continue to raise questions about the long-term effects of antibiotic pollution in waterways, and whether currently harmless water-borne bacteria build up resistance and become harmful (Moore, 2006). Also, the pathways of transference may involve many transfers and long periods of time.

Studies show a range of synthetic steroids concentrations, including 17 α-ethinylestradiol (EE_2) found in oral contraceptives to be, detected in Canadian wastewater treatment plants. The levels range anywhere from 1 – 2 ng/L to 20 ng/L, which are considered extremely low, but concentrations are well within the range that can cause feminization of fish (Metcalfe et al., 2001; 76). Further to this, the estrogenicity of the wastewater treatment plant effluents in the United Kingdom (as measured by vitellogenin production in male fish – primarily a function of natural and synthetic steroid estrogens) has been shown to persist for several kilometres downstream of effluent discharges (Kummerer, 2001; 13). The findings on the effects from exposure to EE_2 will be explored at greater length in an upcoming section.

Higher concentrations of PPCPs in Canada's wastewater treatment effluents in comparison to Europe's may be attributable to a lower degree of wastewater treatment among Canadian municipalities. There is a high incidence of direct discharge of untreated sewage in Canada, resulting in higher concentrations of PPCPs. This is primarily due to older infrastructure and combined sewers, which collect both domestic sewage and storm water. During heavy rainstorm events, the volumes entering the

sewers exceed the treatment capacity of the wastewater treatment plant causing direct discharges of untreated effluents (Metcalfe et al., 2004; 73). Other municipalities use primary treatment technologies in their wastewater treatment plants, and rely upon local hydrological conditions to rapidly dilute the sewage discharges. There are also large numbers of smaller systems that have limited treatment capacity or are operating above capacity. A study assessed the removal of pharmaceuticals, iodinated x-ray contrast media and musk fragrances from municipal wastewater using a pilot ozonation and UV-disinfection plant receiving effluent from a German wastewater treatment plant. By applying 10-15 mg/L ozone (contact time 18 minutes), all the pharmaceuticals investigated as well as musk fragrances and estrone were no longer detected (H. Jones, O. et al., 2005; 413). However, the most common treatment in Canadian municipalities is secondary treatment, using activated sludge, while chlorine and ultraviolet are the most widely used disinfection systems (Metcalfe et al., 2004; 73).

3.3 Surface Water

Tests conducted in Canada have confirmed that lakes, rivers and streams contain trace amounts of PPCPs. The behaviour of these compounds in water is as different as their individual chemistry. Some are volatilized from water, some react chemically with the water itself, some are sorbed to sediments, some are biodegraded, some are photo-degraded, and some diffuse into the water body (Holtz, 2006; 16). In addition, researchers have found data on persistent compounds including anti-epileptics, diagnostic agents such as iodinated X-ray contrast media, caffeine, and clofibrate, all leading to repeated exposure for aquatic organisms (Kummerer, 2004; 4). Chemicals that are continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short (Daughton, 2001; 20). While the risks posed to the health of fish, wildlife and humans are not well understood, there are tell-tale signs of impact. Approximately 30 percent of drugs dissolve only in fat, which enables them to enter cells and move up food chains becoming more concentrated (Batt, July 2006). Degradation processes may vary with factors including turbidity or pH as well as time or season. For instance, the fate of many antibiotics is profoundly affected by pH, while beta-blockers are affected by seasonal conditions (Holtz, 2006; 17). Most

commonly detected in surface waters are acidic pharmaceuticals at trace levels, and detections occur most frequently during low flows (Hebben; July 2006).

The highest concentrations of PPCPs in surface waters were detected at sites close to the discharges from municipal wastewater treatment plants. Metcalfe et al., study (2004) found concentrations of acidic and neutral drugs in surface waters adjacent to discharges of effluents from wastewater treatment plants. Between 1999 to 2002, the prescription anti-inflammatory naproxen and the non-prescription anti-inflammatory ibuprofen were found frequently in surface waters near wastewater treatment plants; one of the carbamazepine metabolites, dihydrocarbamazepine was detected in surface water near the wastewater treatment plant for the city of Peterborough, Ontario. As well, lipid-regulating agents from the fibrate class, including gemfibrozil and bezafibrate have been frequently detected in surface waters near wastewater discharges at concentrations below 200 ng/L (Metcalfe et al., 2004; 77). The study did not specify the distance from the wastewater treatment plant, which would clarify whether the contamination is localized or widely distributed in surface water. Carbamazepine, caffeine and cotinine were the most frequently detected drugs in samples of surface water. Cyclophosphamide, fluoxetine, pentoxyfylline and trimethoprim were detected in some surface water samples, but norfluoxetine was not detected in surface water. Note that norfluoxetine was also not detected in wastewater treatment plant effluents (Metcalfe et al., 2004; 79). Low concentrations, ranging between 5 to 10 ng/L, of clofibric acid, ketoprofen and carbamazepine were detected at open water locations in Lake Ontario and the Niagara River. The majority of PPCP monitoring programs in Canada have been focused on Lake Ontario and Lake Erie, as well as rivers in the Great Lake basin (Metcalfe et al., 2004; 76).

In 2002, an in-depth study examined the concentrations of antibiotics in surface waters located near the discharges from 4 wastewater treatment plants in the Ontario cities of Peterborough, Burlington and Windsor. Samples were collected from the Otonabee River near the effluent discharge from the Peterborough wastewater treatment plant, from Hamilton Harbour near the discharge from the Burlington wastewater treatment plant, from the Detroit River near the discharge from the West Windsor wastewater

treatment plant and from the Little River near the discharge from the Little River wastewater treatment plant. The compounds detected in these Canadian surface water samples include clarithromycin, erythromycin-H_2O, ciprofloxacin, sulfapyridine, sulfamethoxazole and tetracycline (Table V) (Metcalfe et al., 2004; 79).

Analyte	Median (μg l^{-1})	Max (μg l^{-1})	Number of samples collected	Number of samples non-detected
Clarithromycin	0.087	0.536	8	2
Erythromycin-H_2O	0.080	0.838	8	0
Roxithromycin	0.008	0.018	8	2
Ciprofloxacin	0.118	0.400	8	1
Enrofloxacin	Nd[a]	Nd	8	8
Norfloxacin	0.050	0.112	8	4
Ofloxacin	0.094	0.506	8	0
Oxolinic acid	Nd	Nd	8	8
Pipemidic acid	Nd	Nd	8	8
Carbadox	Nd	Nd	8	8
Sulfacetamide	0.064	0.151	8	5
Sulfachloropyridazine	Nd	Nd	8	8
Sulfadiazine	0.019	0.019	8	7
Sulfadimethoxine	Nd	Nd	8	8
Sulfaguanidine	Nd	Nd	8	8
Sulfamerazine	Nd	Nd	8	8
Sulfamethazine	0.363	0.363	8	7
Sulfamethizole	Nd	Nd	8	8
Sulfamethoxazole	0.243	0.871	8	0
Sulfamethoxypyridazine	Nd	Nd	8	8
Sulfamoxole	Nd	Nd	8	8
Sulfapyridine	0.081	0.228	8	0
Sulfaquinoxaline	Nd	Nd	8	8
Sulfathiazole	Nd	Nd	8	8
Sulfisomidine	Nd	Nd	8	8
Sulfisoxazole	0.019	0.034	8	3
Chlorotetracycline	Nd	Nd	8	8
Doxycycline	0.038	0.046	8	6
Oxytetracycline	Nd	Nd	8	8
Tetracycline	0.151	0.977	8	1

[a] Not determined.

Table V. Concentrations of antibiotics in surface water samples collected in 2002 near wastewater treatment discharges in 4 locations in Canada (Source: Metcalfe et al., 2004)

These results are similar to the types of antibiotics detected in surface waters in Europe and the rest of North America (Trudeau et al., 2005; 477). It is very possible that the sources of some of these antibiotics are not only human sewage effluents but also livestock operations where antibiotics are used in feed.

In a separate 2002 study, the ratios of the concentrations of selected neutral and acidic drugs of wastewater treatment plant final effluents in Windsor (i.e., Little River wastewater treatment plant) and Burlington relative to surface water immediately adjacent to the wastewater treatment plant, were examined (Figure 1 – lines representing ratios 1.0 and 0.1 for these parameters are shown on the figure). For the Little River, the ratios for concentrations in surface water and effluent ranged between 0.45 to 1.21; that is, generally distributed around a 1:1 relationship (Metcalfe et al., 2004; 79). The conclusion that can be drawn is that there was virtually no dilution of drugs discharged from the Little River wastewater treatment plant into the low flow system. Further to this study, the presence of drugs was investigated in the Little River and the Detroit River (Figure II). The Little River is a small tributary that flows into the Detroit River approximately 500 m downstream from the wastewater treatment plant (i.e., site 6).

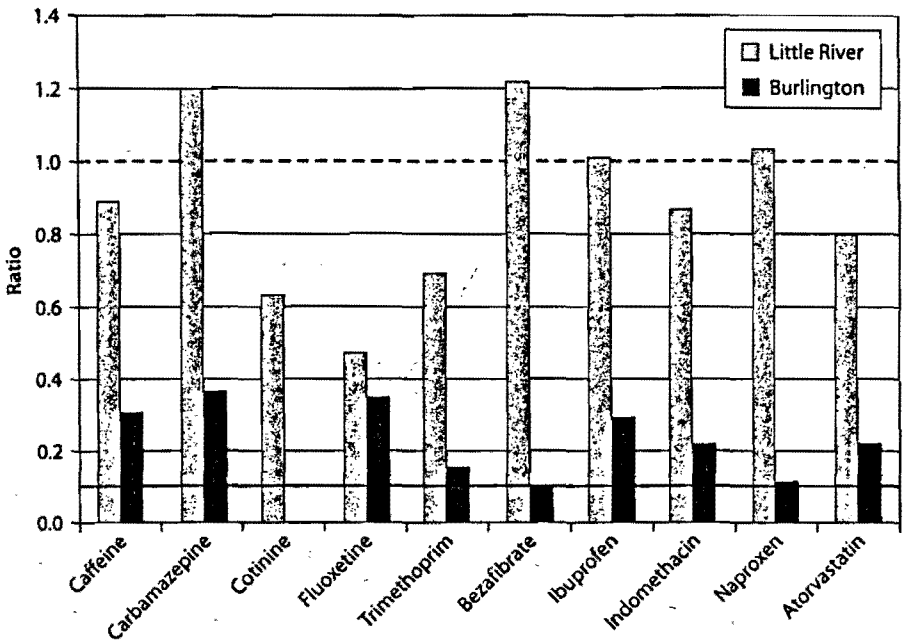

Figure I. Ratio of the concentrations of selected neutral and acidic drug samples collected in 2002 of wastewater treatment plant final effluent and surface water immediately adjacent to the wastewater treatment plant (Metcalfe et al., 2004)

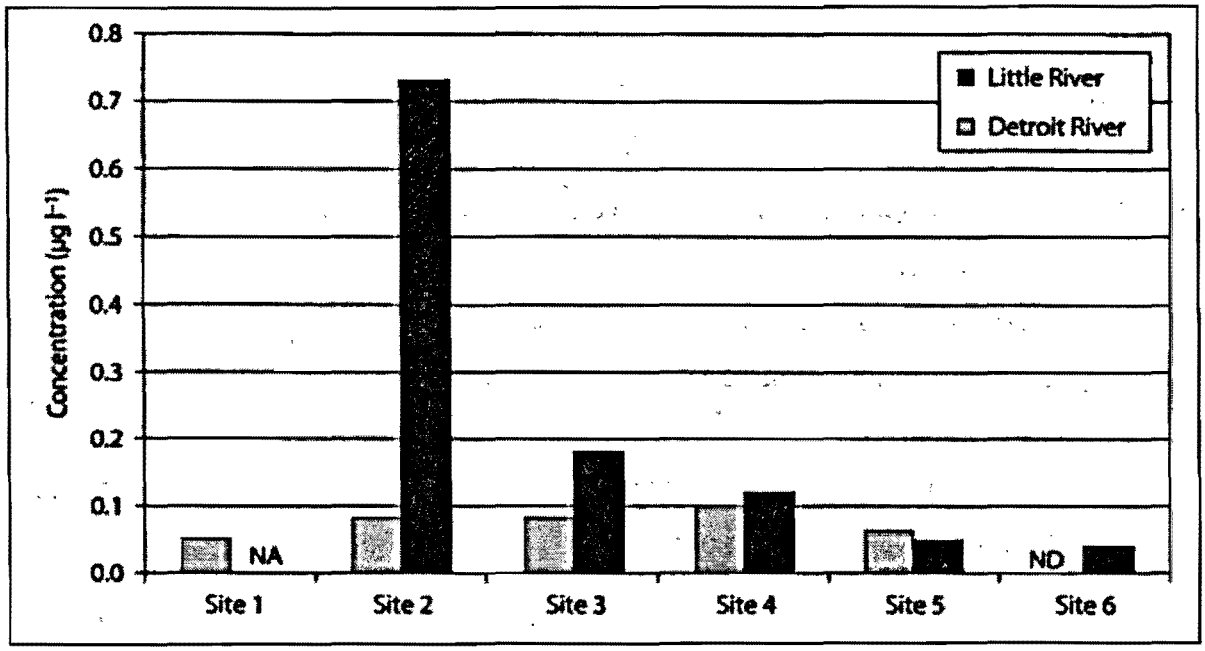

Figure II. Concentrations of naproxen in samples collected in 2001 at 6 sites at 100 m intervals in the Little River and the Detroit River. These sites were downstream of the discharge of the Little River wastewater treatment plant and the West Windsor wastewater treatment plant, respectively in Windsor, Ontario (Source: Metcalfe et al., 2004)

This shows the concentrations of naproxen in samples collected in 2001 at 6 sites at 100 m intervals downstream in the Little River and the Detroit River. The concentrations of naproxen in the Little River remained relatively constant at sites 1 through 5, located at 100 m downstream of the wastewater treatment plant (Metcalfe et al., 2004; 81). Please note the author(s) have indicated in the chart that Little River is the black bar and Detroit River is gray bar, when in fact, based on the description, Little River is represented by the gray bar and Detroit River is represented by the black bar. The concentrations of naproxen fell below detection limits where the Little River discharges into the Detroit River, due to high dilution in this dynamic river system. Moreover, a similar plot for the ratios of concentrations in the effluent from the wastewater treatment plants for the city of Burlington, and surface water at the discharge site in an embayment of Lake Ontario (i.e., Hamilton Harbour) shows ratio varying from 0.1 to 0.35, indicating a greater degree of dilution.

3.4 Drinking Water

Relative to sewage effluents and surface waters, a much smaller number of PPCPs have been detected in drinking water. PhACs found in drinking water are at extremely low concentrations compared to therapeutic doses. To put it into perspective, for most drugs, commonly prescribed in doses ranging from several to several hundred milligrams, a person would have to drink thousands or even millions of litres of surface water to ingest an amount comparable to the concentrations in that one pill (Holtz, 2006; 15). The potential health risks as a result of human consumption are likely to be highly variable, considering the spatial and temporal factors that influence pharmaceuticals in raw water uptake (Metcalfe et al., 2004; 85).

Despite the low levels of exposure, there are still concerns about PhACs in treated potable water. There are many unanswered questions pertaining to (the consumption of) chronic, low-level concentrations via drinking water, such as: What are the effects from the mixtures of drugs in drinking water? What is the exposure to a fetus in pregnant women. An area of concern would be those drinking water treatment plants located downstream or in close proximity to a wastewater treatment plant, which may be the case for many Canadian municipalities such as those that use the Grand River (Ontario) watershed as the intake source of raw water. Several investigations have reported on the human risks associated with exposure to drinking water contaminated with PhACs, including EE_2, phenoxymethylpenicillin and cyclophosphamide (Metcalfe et al., 2004; 83). The endpoints of human effects that were evaluated in this study were endogenous estrogen synthesis, allergic reactions and genotoxic carcinogenicity. In the cases cited, the risk was assessed to be negligible (Metcalfe et al., 2004; 83).

Recent research found that the type of treatment process employed will determine the removal of PPCPs and ultimately the levels in drinking water. One study looked at neutral drugs in drinking water for the City of Windsor, Ontario. It was initiated as part of a broader investigation of PPCPs and pesticides in surface waters of the Detroit River. Based on previous studies on neutral drugs in effluents from a wastewater treatment plant upstream of the A. H. Weeks water treatment plant, a suite of eight major neutral drugs (i.e., carbamazepine, cotinine, caffeine, cyclophosphamide, fluoxetine,

norfluoxetine, pentoxyfylline, trimethoprim) and nine major acidic drugs (i.e., bezafibrate, clofibric acid, diclofenac, fenoprofen, gemfibrozil, ibuprofen, indomethacin, ketoprofen, naproxen) were assessed in raw and treated drinking water. Like many treatment plants, the A. H. Weeks water treatment plant treats drinking water by flocculation with aluminum sulfate, post-sedimentation and dual filtration (with anthracite and sand), and ozone disinfection (Metcalfe et al., 2004; 83). In addition, the results of a pilot plant on site are assessed. The pilot plant had the same basic treatment process with the exception that the one flow stream has ozone treatment and a parallel stream is without (Figure III).

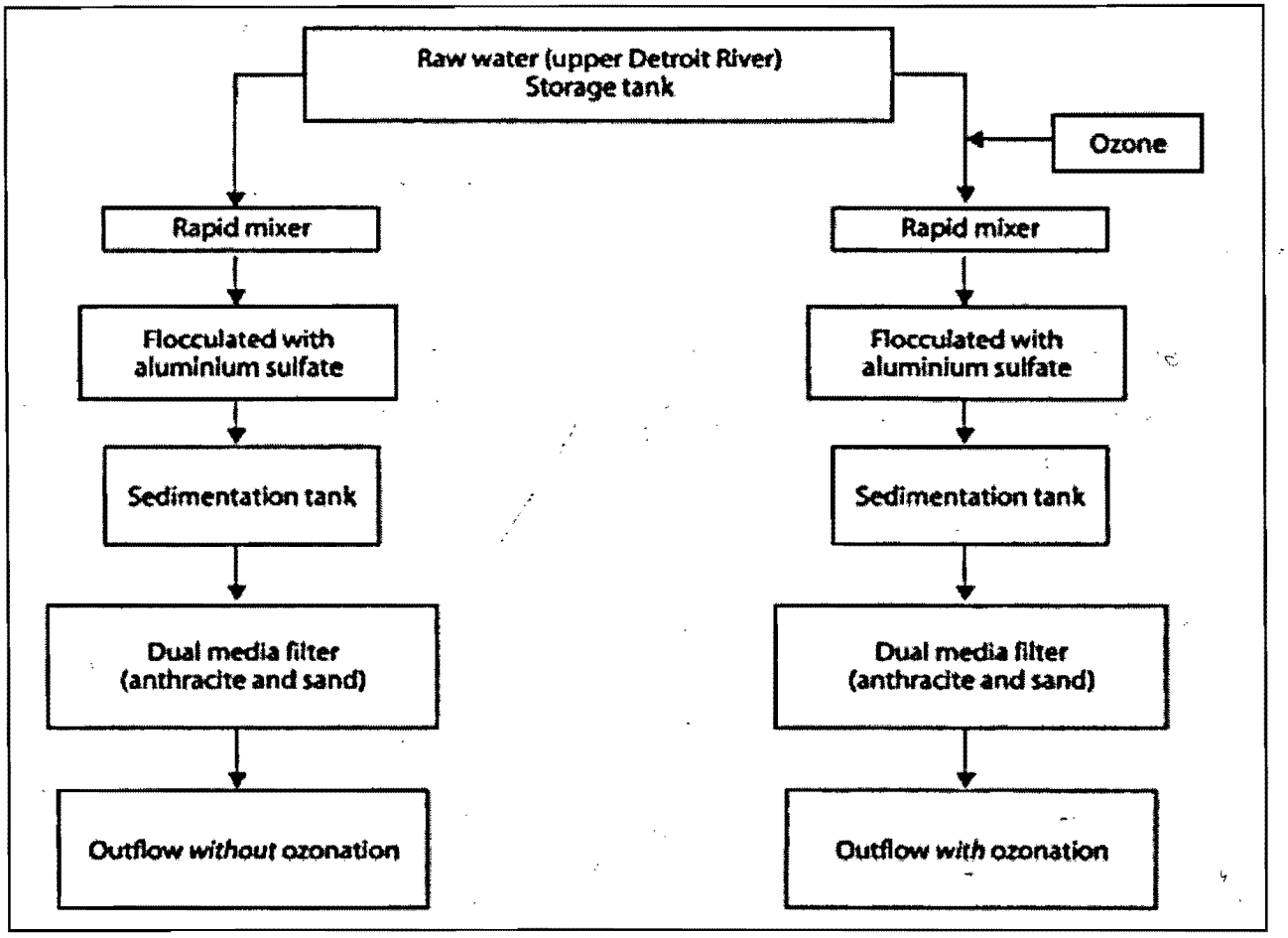

Figure III. Flow diagram schematic of the pilot plant process for water treatment at the A.H. Weeks plant, City of Windsor, Ontario (Source: Metcalfe et al., 2004)

Carbamazepine and cotinine were detected in the raw water at average concentrations of 1.6 and 0.3 ng/L, respectively (Metcalfe et al., 2004; 83). The removal of carbamazepine and cotinine with ozone treatment ranged from 57 to 67 percent, respectively, whereas removal without ozone treatment was 13 percent and zero percent, respectively. In the same study, the effects of changes in the condition of raw water (e.g., temperature, pH and turbidity) over an annual seasonal cycle on the removal of neutral and acidic drugs, were examined. Regardless of the seasonal changes in raw water parameters, the degradation of the detected PhACs with ozone treatment remained greater than 75 percent, while no significant degradation was found without ozone treatment (Metcalfe et al., 2004; 83). A journalistic investigation instigated by CTV News in 2003, found detectable concentrations of both carbamazepine (in

Brooks, Alberta, Montreal and Hamilton) and gemfibrozil (in Portage La Prairie, Manitoba) in 4 out of the 10 Canadian cities tested that all used advanced water treatment such as ozone (Holtz, 2006; 18). Overall, sand filtration and flocculation coupled with iron chloride were ineffective for the removal of selected drugs, while ozonation and filtration with granular activated carbon was very effective.

3.5 Aquatic Biota

Little information is available on the biological effects of PPCPs on aquatic organisms. The vast numbers of drugs that are used make it difficult to predict the possible effects to non-target species. Little is known about the effects of these substances on non-target organisms, many of which differ from mammals in their receptor sensitivity, and in the roles various metabolic pathways play in their development and reproduction. Endpoints, such as neurobehavioral changes, can be very subtle but nonetheless lead to unanticipated, profound outcomes on non-target populations (National Water Research Institute, 2007; 2). Since most pharmaceuticals are designed not to bioaccumulate in human tissues, there is little potential for them to do the same in tissues of exposed fish, but bioconcentration in the blood might be a possibility (Trudeau et al., 2005; 478). There are some PPCPs such as clofibric acid, which are persistent (just) as organochlorine persistent organic pollutants (e.g., DDT), simply because their source continually replenishes any removed and effectively sustains perpetual, multi-generational life-long exposures for aquatic organisms (Daughton, 2001; 14). With the exception of certain drugs such as chemotherapy agents and mutagenic antibiotics, drugs used in human applications usually have low acute toxicity which is one of the criteria for approval of drugs initially. Therefore, the biological impacts will likely occur as a result of the actions of these drugs on fish or through similar mechanisms by which they act in humans (Trudeau et al., 2005; 478).

Some pharmaceuticals are related to a group of chemicals whose effects are to disrupt the endocrine systems of living organisms. Many hormonal and metabolic systems targeted by pharmaceuticals (i.e., drugs principally for humans, livestock, pets) are conserved in vertebrates, drug effects on aquatic animals such as fish and frogs can be expected (Trudeau et al., 2005; 478). In fish, among other wildlife, effects have included

reproductive impairment or failure, deformities, and feminization (Holtz, 2006; 20). Lack of comprehensive exposure data (which for the aquatic environment, in contrast to the terrestrial environment, can sometimes be inferred simply from occurrence/concentration data) is a critical limitation to the advancement of risk assessment (Daughton, 2001; 6).

3.5.1 Effects of EE_2 on Aquatic Biota

One of the best pieces of evidence of effects from exposure to PPCPs is drawn from studies of EE_2 found in oral contraceptives. EE_2 is designed to be extremely potent at the estrogen receptor, hence environmental exposure to low concentrations has the potential to disrupt the development of normal endocrine and reproductive function when exposure occurs during critical periods in an organism's development (Foran et al, 2002; 68). These compounds have the ability to modulate endocrine processes not only in humans, the intended users, but are also known to affect non-target organisms such as fish, reptiles and birds (Sanderson et al., 2004; 36). This is especially evident for fish inhabiting waters that receive effluents from wastewater treatment plants which are a complex mixture containing estrogens and estrogen mimics that are known to affect the reproductive health of wild fish (Kidd et al., 2007; 8897).

There are a number of laboratory studies that indicate male fish are being feminized at low-level, chronic exposures. Based on these observations, the possibility exists that the concentrations of estrogens observed in freshwaters can impact the sustainability of wild fish populations (Kidd et al, 2007; 8897). The plasticity of gonadal development in fish, which contrasts with the more stable patterns found in higher vertebrates, may make fish more susceptible to EDSs that affect reproductive development (Van Aerle et al., 2002; 424). Sexual differentiation, which is the physical determination of the genetic sex, can occur at different times for different fish species. This can take place from within a few weeks of hatching, as occurs in salmonids, to a few months after hatching, as occurs in some cyprinid fish (Van Aerle et al., 2002; 424). Hence, when fish embryos are exposed to elevated levels of estrogens during these critical times, the implications can be unintended.

There have been various ways of determining the impact of exposure to EE_2. The majority of the studies looked at the induction of vitellogenin in male fishes, which is used as a biomarker of exposure to synthetic estrogens. In fish, vitellogenin is normally found in the blood of maturing females, whereas the levels in male or juvenile fish are very low (Larsson et al., 1999; 91). Other endpoints and ways of measuring the nature of impact included gross development and growth, reproductive parameters such as gonad development, sex determination and reproductive maturity (Lange et al., 2002; 1222). Furthermore, these studies reveal that the length of exposure and timing of exposure relative to development are critical in determining the level of sensitivities to endocrine disruption.

Fish inhabiting waters that receive municipal effluents are exposed to natural estrogens 17 beta-estradiol (E_2) and estrone (E_1) as well as EE_2 which are believed to be responsible for, or contribute to, the feminized responses in some wild fish (Nash et al., 2004; 1725). Laboratory studies have shown that the concentrations of E_2 (up to 80 ng/L), and E_1 (up to 220 ng/L) in treated sewage effluents entering United Kingdom rivers are sufficient to induce the vitellogenic effects observed in caged fish (Van Aerle et al., 2002; 242). Generally, natural steroidal estrogens or phytoestrogen, are found in surface water in greater concentrations than EE_2. However, the potency of EE_2 in fish is 10 to 50-fold higher than that of E_2 and E_1 in vivo, due to its longer half-life and tendency to bioconcentrate (Nash et al., 2004; 1725).

In fish, exposure to EE_2 and EDSs alters their reproductive physiology and morphology, which may result in the induction of female-specific proteins in male fish, induction of gonopodia in females, reduced sperm counts, skewed sex ratios, and prevalence of intersexulaity (Nash et al., 2004; 1725). There is evidence of disruption in gonadal development by the presence of both male and female gonadal tissues (intersex) and decreased gonadosomatic indices (GSIs) (Kidd et al., 2007; 8897). The implication of intersexed male fish is in reduced reproductive success due to decreased sperm production. Studies have found that only 0.1 ng/L of EE_2 induces vitellogenin yolk precursor; 0.1 – 15 ng/L that can affect normal sexual development and differentiation; 2 – 10 ng/L can affect fecundity; 10 ng/L can affect reproductive behaviour; and 1 – 10

ng/L can reduce the fertilization success or viability of embryos from exposed adults (Nash et al., 2004; 1725). While the laboratory studies have shown decreased reproductive success of fish exposed to < 1 – 5 ng/L of EE_2, it is questionable whether this response would be observed in wild populations and whether it would result in a subsequent decline in abundance (Kidd et al., 2007; 8897).

A recent study was done examining the fathead minnow in an experimental lake. This was a 7-year, whole-lake study at the Experimental Lakes Area in northwestern Ontario, Canada, where the effects of EE_2 from the subcellular-level to the population level on fathead minnows were assessed (Kidd et al., 2007; 8897). The results clearly implicated a reduction of reproductive success of the fish population from chronic exposure to EE_2. The concentrations of EE_2 achieved in the experimental lake during the 3 years of additions were within the range of those observed in untreated and treated municipal wastewaters (Kidd et al., 2007; 8897). EE_2 led to feminization of males through production of vitellogenin messenger ribonucleic acid (mRNA) and protein, continued production of vitellogenin in females beyond the normal breeding season, impacts on gonadal development, as evidenced by intersex in males and altered oogenesis in females, and a near extinction of this species from the lake (Kidd et al., 2007; 8900). Fathead minnow was the first to show population collapse in this experiment. This is likely because of its short life-cycle, and implies that short-lived fish species may generally be at greatest risk from exposure to estrogens and their mimics (Kidd et al., 2007; 8900).

This study used environmentally relevant concentrations of EE_2 to demonstrate the impact to the aquatic environment in municipal wastewaters. Measuring vitellogenin mRNA and protein was an endpoint used to assess the subcellular responses of fathead minnow from Lake 260 to EE_2 additions (Kidd et al., 2007; 8898). There were some expected results, such as elevated levels of vitellogenin when compared with reference lake data prior to addition of vitellogenin. Whole-body homogenates of males from Lake 260 had concentrations of vitellogenin that were 3 orders of magnitude higher than reference samples, and this response was sustained in each of the 3 years of EE_2 additions; the female fathead minnow also produced higher levels of vitellogenin after

exposure (reference lake fish had 2.5 percent of the vitellogenin concentrations than in treated fish from Lake 260 (Kidd et al., 2007; 8897). The elevated levels of vitellogenin production in female fathead minnow from Lake 260 was followed by delayed ovarian development) (Kidd et al., 2007; 8899).

This study produced significant findings revealing the adverse impacts from exposure to EE_2 on male fathead minnows (Figure IV). Over the 3 years of dosing, male fathead minnow from Lake 260 had mean ± SD normalized liver vitellogenin mRNA values ranging from 0.422 ± 0.685 to 1.22 ± 0.181; values for males from the 2 reference lakes were on average < 0.1 to 1.6 percent of those for the EE_2-exposed males (Kidd et al., 2007; 8897). As a matter of fact, the males from Lake 260 had vitellogenin mRNA values (0.904 ± 0.437) that were more than an order of magnitude higher than female fish (0.045 ± 0.048) collected from the reference lakes during the same time periods (Kidd et al., 2007; 8897). Testicular tissues of all of the male fathead minnows collected during the first spring after EE_2 additions displayed delayed spermatogenesis, widespread fibrosis, and malformations of the tubules (Kidd et al., 2007; 8897). Testicular germinal tissue from all EE_2-exposed males consisted primarily of spermatogonia instead of the spermatocytes that were normally observed at this time of year in the reference lakes and in Lake 260 before EE_2 additions (Kidd et al., 2007; 8897). In the spring of 2002, the GSI for males from Lake 260 averaged 0.40 ± 0.21 percent, which was well below the GSI values of 1.39 ± 0.38 percent and 2.27 ± 0.41 recorded for males from reference Lakes 114 and 442, respectively. This arrested testicular development continued in 2003 and 2004, and 4 of 9 males captured in the spring of 2003 had ova-testes with the presence of primary-stage oocytes (Kidd et al., 2007; 8897).

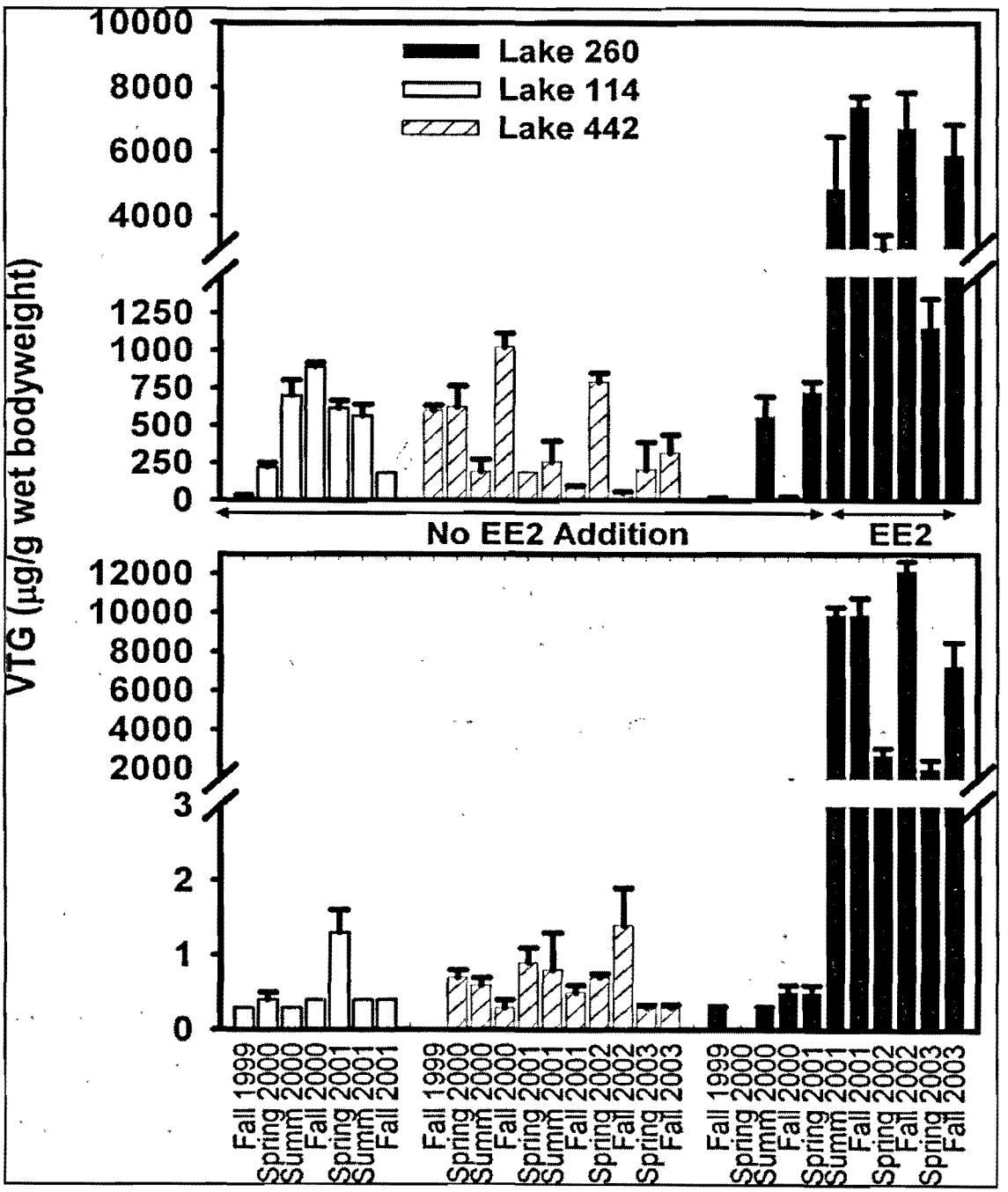

Figure IV. Mean ± SE (n = 4–7) VTG concentrations in whole-body homogenates of male (*Lower*) and female (*Upper*) fathead minnow captured in 1999–2003 from reference Lakes 114 and 442 and from Lake 260 before and during additions of 5–6 ng·L^{-1} of EE2 (low catches of fish in Lake 260 in 2004 and 2005 did not allow for these analyses in the latter 2 years of the study). (Source: Kidd et al., 2007).

The fathead minnow population in Lake 260 collapsed in the fall of 2002, after the second season of EE_2 additions, because of a loss of young-of-the-year (Kidd et al.,

2007; 8899). This reproductive failure was also observed in the third season of amendments and continued for an additional 2 years after the EE_2 additions had ceased, although a few small individuals were caught each year, indicating some reproduction was occurring (Kidd et al., 2007; 88979). In addition, the mean ± SE size of adult fish from Lake 260 increased from 50 ± 0.28 mm (n=300) in 2001, just after the first EE_2 additions, to 62 ± 0.18 mm (n=263) in the fall of 2003, because of a shift in the age structure of the remaining population (Kidd et al., 2007; 8899). The reproductive failure and near extirpation of fathead minnow in Lake 260 has not yet been observed in the longer-lived pearl dace in this system, and this suggests that life-history characteristics such as lifespan are important determinants of a species' risk from exposure to estrogens (Kidd et al., 2007; 8897).

An earlier 2001 study examined the developmental and reproductive patterns by investigating the full life-cycle that include a measurement of vitellogenin, reproductive and developmental parameters. This was achieved by defining the EE_2 dose-response and the No Observed Effects Concentrations (NOEC) for EE_2 over a multigenerational exposure (two generations), and second, by addressing biomarkers of endocrine disruption, such as changes in vitellogenin and gonad histology (Lange et al., 2002; 1217). EE_2 had expected effects on the early stages of development, with a significant decrease in F0 (parent) larval growth after 28 days post-hatch, giving Lowest Observed Effects Concentration (LOEC) and NOEC values of 16 and 4.0 ng/L, respectively (Lange et al., 2002; 1222). After 56 days post-hatch, the adverse effect of EE_2 on larval growth was increasingly severe, giving LOEC and NOEC values of 4.0 and 1.0 ng/L, respectively (Lange et al., 2002; 1222). Continued exposure of F0 fathead minnows to EE_2 led to further general retardation of maturation and development of secondary sexual characteristics (Lange et al., 2002; 1222). Fish exposed to 4.0 ng/L showed no male secondary sex characteristics at any age (while the control fish and the fish at less than or equal to 1.0 ng/L became sexually mature after 120 days post-hatch), and at greater than or equal to 16 ng/L, fish showed abnormal development in respect of growth and secondary sexual characteristics (Lange et al., 2002; 1222). After 172 days post-hatch, histological analysis showed that all fish from the 4.0 ng/L group had

gonads containing only ovarian tissue (Lange et al., 2002; 1222). In F0 fish exposed to 4.0 ng/L, 100 percent of individuals had all female gonads, supporting the conclusions that there was a dramatic inhibition of breeding after long-term exposure to EE_2 at > 1.0 ng/L (Lange et al., 2002; 1224). Extremely high vitellogenin levels occurred only in those exposure groups which also exhibited severe developmental and reproductive impairment with NOEC values for all these endpoints being in close agreement; equally, fish developing and reproducing normally also did not show abnormal levels of vitellogenin in their tissues (Lange et al., 2002; 1225). In summary, life-cycle exposure to low concentrations of EE_2, produced concentration-related impacts on growth, development, sexual development, and reproductive health. Overall, for the endpoints monitored during this study, the biologically derived NOEC was 1.0 ng/L (Lange et al., 2002; 1226).

One of the more drastic implications of environmental exposure to EE_2 is the potential for population–level consequences on reproductive success. A study was conducted in a laboratory aimed at measuring the impacts on reproductive success in zebrafish populations over multiple generations and the mechanisms of reproductive impairment using environmentally relevant concentrations of EE_2 and E_2. In order to accomplish this, the multigenerational full life-cycle exposure was considered, including all relevant life stages and the developmental end point (Nash et al., 2004; 1726). Examining these stages would be nearly impossible in wild fish populations due to all the variables. A major goal of this study was to determine which stages or reproductive components are relatively most sensitive to endocrine disruption in terms of population-level impairment or failure (Nash et al., 2004; 1726).

The nominal estrogen doses used for this study were 0.5, 5, and 50 ng/L for EE_2 and 5 ng/L for E_2. The impacts of estrogen exposure on reproductive success during multigenerational exposure were assessed. The short term exposure to 50 ng/L EE_2 in the F0 generation (parent) caused a time-related reduction in egg production and egg viability to 14 hours post-fertilization and no survival of their F1 offspring to 100 hours post-fertilization (Nash et al., 2004; 1728). After 10 days exposure there was complete reproductive failure (no egg production) in the 50 ng/L EE_2 exposure group and these

results support previous findings for high dosage, short-term effects of EE_2 (Nash et al., 2004; 1728). In complete contrast, life-long exposure (210 days post-fertilization) to 5 ng/L EE_2 resulted in complete reproductive failure in the F1 generation, with no viability in the eggs at 14 hours post-fertilization; there was no viable eggs in almost 12,000 spawned (Nash et al., 2004; 1728).

Studies have shown that while there are no clear and immediate human health risks, there are potential for aquatic effects, particularly on reproduction. Based on existing evidence, there is enough concern to raise the question of environmental management of PPCPs. The following section will explore some of the government regulatory actions that have been implemented to address some of these concerns.

4. Regulations on Pharmaceuticals and Personal Care Products

4.1 Canadian Government

Currently, drug safety assessments for human and veterinary pharmaceutical products in Canada are evaluated under the federal Food and Drugs Act. These assessments have not been related to environmental protection. Regulatory initiatives concerning PPCPs in the environment are relatively recent. Changes have been made to the CEPA, which makes it a requirement for manufacturers or importers of new substances to provide data on substances for the government's assessment. If a company intends to manufacture more than 20 kilograms per year of a new substance, it must notify the government and submit information for review by government scientists (Health Canada, 2006). Under CEPA, the government must use a preventative approach to assess and manage the risks posed by new substances that may be toxic. The CEPA deadlines for this work range from 5 to 120 days. Essentially, Environment Canada focuses on the risks to the environment, while Health Canada focuses on risks to human health (Health Canada, N/A). The evaluation of human products is based on the assessment of chemicals in these drugs (Marsalek, 2008; 124).

Human pharmaceuticals, among other Food and Drug Act products, are subject to the notification requirements of the New Substances Notification Regulations (Chemicals and Polymers) [NSNR (Chemicals and Polymers)] of CEPA since September 2001.

NSNR (Chemicals and Polymers) are an integral part of the federal government's "cradle to grave" management approach to toxic substances. Before CEPA was passed, the government took an inventory of substances already in use in consumer goods and manufacturing processes in Canada, which are classified as existing substances. Any substances that were not listed in the inventory are considered a new substance. If Health Canada scientists conclude that a new substance poses no health risks to the public and Environment Canada scientists conclude no risk to the environment, the import of manufacture of the substance can begin. On the contrary, if there is reason to suspect that a new substance may pose a health risk, Health Canada takes preventative action to manage the risks, by imposing controls on the manufacture, import, use, release and/or disposal of a substance (Health Canada, 2006).

Both Environment and Health Canada are working to develop Environmental Assessment Regulations (EAR), which will require substances, contained in products regulated under the Food and Drugs Act, such as pharmaceuticals/radiopharmaceuticals/therapeutic products, personal care products, cosmetics, biologics/generic therapies, veterinary drugs and medical devices to comply with both environment assessment requirements and current health and safety criteria. As the development of the regulations continues, Health Canada is conducting environmental risk assessments for these substances under the NSNR (Chemicals and Polymers).

As of September 14, 2001, Health Canada conducted environmental assessments on substances in products regulated under the Food and Drug Act in accordance with CEPA and the NSNR (Chemicals and Polymers). Substances existing in Food and Drug Act products that were on the market between 1987 and September 13, 2001, but which are not already listed on the Domestic Substances List, will be assessed under the new EAR, once they are finalized (Health Canada, May 2006). If a new substance may pose a risk to the environment or human health, CEPA 1999 empowers the Ministers of the Environment and Health to intervene prior to or during the earliest stages of its introduction into Canada.

Under the proposed EAR, Health Canada will take a series of risk assessment and risk management actions. Health Canada officials will attempt to obtain any available information from proponents relevant to an assessment of "toxic." Under CEPA, a substance is considered "toxic" if it enters or may enter the environment in amounts that may pose a risk to human health, the environment (such as fish or wildlife), and the environment upon which life depends (such as water, soil and air) (Environment Canada, May 2006). The Environmental Assessment Unit of Health Canada will evaluate this information in order to determine appropriate action. If, following the initial evaluation, the substance is not suspected to be harmful to the environment it will be further evaluated once the new regulations are in place. If additional information is required in order to make an assessment, the Environmental Assessment Unit will obtain additional information, drawn from the NSNR (Chemicals and Polymers) schedules, on these substances and, where appropriate, recommend control measures to Environment Canada (Health Canada, N/A).

Since September 2001, the Environmental Assessment Unit has received approximately 400 new substance notifications for substances in Food and Drug Act products – 62 percent have been cosmetic ingredients and 21 percent have been pharmaceutical substances (National Water Research Institute, 2007; 16). The majority of submissions, however, have been notified at the first notification level – a level that does not require the generation of environmental fate, distribution or effects data. This lack of experimental data is only one of the many challenges facing Health Canada in determining the risks these substances might pose to the environment. Other limitations that need to be considered include the appropriateness of current notification trigger quantities, the types of fate and effects data that should be generated and the high degree of uncertainty associated with the use of existing fate/effects models and generic release scenarios. As a result, the research priorities for the Environmental Assessment Unit have focused on filling these information gaps (National Water Research Institute, 2007; 16). Specifically, the need for additional environmental data on "classes" of substances would be beneficial, the suitability of existing physical, chemical, fate and effects models must be more closely investigated and, the significance of subtle, chronic effects and how they are incorporated into the risk

assessment process should be considered (National Water Research Institute, 2007; 16).

Questions are being raised about whether current approaches to risk assessment of "priority pollutants" are too narrow in perspective. They normally cover single substances and not for mixtures. New chemicals currently undergo a very limited screening while approaches for assessing older chemicals and their potential for complex mixtures have not yet been determined. The potential for these substances to cause a variety of physiological responses in non-target species are concerns (Metcalfe et al., 2004; 86). Traditionally, risk assessment and regulations move away from cumulative effects on humans and wildlife. In a number of cases, it is the cumulative effects that lead to environmental changes in unintended ways. However, the primary objectives of risk assessment, including toxicology, have been human morbidity and mortality (i.e., acute toxicity, carcinogenicity, teratogenicity, and mutagenicity) with less focus on subtle but nonetheless unanticipated, insidious outcomes including neurobehavioral, immunological, and endocrine homeostasis (Daughton; 2001; 4). However, the synergistic and cumulative time-course effects cannot be fathomed unless our understanding of the aggregate "exposure universe" is understood (Daughton; 2001; 5).

While the magnitude of drug disposal as a source of environmental pollution is not yet sufficiently understood, it may be necessary to take a precautionary approach in light of uncertainty on the potential for serious effects. CEPA commits the government to implementing the precautionary principle in decision-making:

> *Whereas the Government of Canada is committed to implementing the precautionary principle that, where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation (Preamble CEPA 1999; paragraph 2(1)(a)).*

Programs to manage PPCPs such as medication take-back programs incorporate the precautionary principle by requiring proactive source reduction measures that could

decrease the amount of pharmaceutical residues from entering the aquatic environment, in the face of scientific uncertainty. The direct cause and effect relationship of PPCPs in the environment are not yet fully established; however, these stewardship programs places the onus on the pharmaceutical manufacturers, who create the hazards, to take responsibility. Furthermore, a proactive, voluntary holistic stewardship program for PPCPs would be preferable to a reactive, prescriptive regulatory program (Daughton, 2003; 763).

4.1.1 Provinces

Other levels of government play regulatory roles aimed at protecting the environment from various toxic substances, including PPCPs. Provinces have permitting and licensing roles for pesticide use, industrial emissions, hazardous waste and protecting drinking water quality. However, these powers are best suited to regulating easily specified actions, products, or chemicals (Holtz, 2006; 35). In a number of provinces, pharmaceutical waste generated by the production of pharmaceuticals, is defined as hazardous waste. For instance, in Ontario's Regulation 347, under the Environmental Protection Act, acute hazardous wastes are those found in concentrations greater than 0.3 percent and are listed as epinephrine, nicotine, nitroglycerin, physostigmine and warfarin in Schedule 2A; and characteristic waste chemicals in Schedule 2B are wastes found in concentrations of less than 0.3 percent and are listed as chlorambucil, cyclophosphamide, hexachlorophene, melphala, reserpine and warfarin (Environmental Advisory Group, N/A). Despite the limited aforementioned definition, most pharmaceutical manufacturers and importers treat all unused and expired pharmaceutical products as hazardous and send them for incineration. This is primarily because of the tremendous liability risks associated with product that might find itself in the wrong hands (Environmental Advisory Group, N/A). Issues relating to consumer disposal of PPCPs and human excretion into the sewage system, remain unaddressed.

4.1.2 Municipalities

Many Canadian municipalities have sewer by-laws which prohibit putting various substances into the sewer systems, and may be useful to prevent some EDSs such as

birth control pills from being discarded down drains and toilets (Holtz, 2006; 33). While by-laws are not consistent across municipalities, many have begun to recognize and classify pharmaceutical waste as a hazard. Some have lumped this waste into the Household Hazardous Waste stream to help consumers define and dispose of it properly (Environmental Advisory Group, N/A). More attention is paid to good stewardship in the pharmaceutical industry by ensuring that waste from the manufacturing process is duly pretreated before discharging into public sewers (Marsalek, J., 2008; 125).

4.2 Europe

Europe has taken more regulatory action to antibiotics, compared to Canada. In 1986, Sweden banned all animal growth promoters in response to concerns about antibiotic resistance in human pathogens. The worry was especially heightened about animal use products that came from families of antibiotics that were vital for human medicine, such as vancomycin (Holtz, 2006; 31). Denmark, which also grown fearful about its rising rates of vancomycin-resistant infections, banned vancomycin's animal-use relative avoparcin as well as the streptogramin, virginiamycin. The European Union eventually followed suite banning all remaining animal growth promoters associated with human medicine, specifically tylosin, bacitracin, and spiramycin (Holtz, 2006; 31). In 2003, the European Union went even further by implementing regulations designed to phase out antibiotic animal growth promoters entirely by 2006. The World Health Organization set up the Global Strategy for Containment of Antimicrobial Resistance (AMR). In contrast, no regulatory actions are being taken by Canada on AMR and animal use of antibiotics as growth promoters. Health Canada's Veterinary Drugs Directorate, which is the regulatory agency involved, is still gathering and assessing information before developing new policies on the issue. One recommendation of Health Canada's *Report of the Advisory Committee on Animal Use of Antimicrobials and Impact on Resistance and Human Health* in 2002 was to "Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely if ever used in human therapy; and not likely to impair the efficacy of any other prescribed

antimicrobial for human infections through the development of resistant strains." (Holtz, 2006; 32). Regrettably, this has not yet been done.

The European Union nations are considered world leaders in developing guidelines for risk assessments of pharmaceuticals. The environmental risk assessment procedure in Europe is comprehensive and a phased approach. During the initial stage of risk assessment, the objective is to determine whether the medicinal product is unlikely to represent a risk to the environment or to identify and characterize the potential risks. If relevant experimental data (e.g., metabolism) can be obtained from other parts of the dossier, these should be used in the assessment, and such studies therefore need not be repeated (Olejniczak and Spindler, 2001; 276). Any existing information on synergistic effects needs to be included. If the medicinal product exhibits potential risks to the environment, the applicant is required to propose appropriate precautionary and safety measures to be applied to the product if the product is administered to patients and/or for the disposal of waste products. Emphasis should be placed on the parent compound and/or metabolite(s), as determined by a human excretion profile (Olejniczak and Spindler, 2001; 276). The environmental risk assessment consists of two primary phases. Phase I entails assessing the exposure of the environment to the drug substances. Substances of low environmental risk will require a justification within the Expert Report. Certain substances including EDSs may need to be addressed irrespective of the quantity released into the environment. Phase II essentially involves compiling information about the physical/chemical, pharmacological and/or toxicological properties obtained and assessed in relation to the extent of exposure of the environment and evaluation of the possible fate and effects (Olejniczak and Spindler, 2001; 276).

Over the last decade, steps to harmonizing pharmaceutical regulations and testing guidelines among international communities have been increasing. This undertaking is being spearheaded by the International Conference of Harmonisation of Pharmaceuticals for Human Use (ICH). However, perhaps mainly because of overlying differences in regulation (directives and acts) between the ICH regions, environmental risk assessment has not been included in the harmonization process (Olejniczak and

Spindler, 2001; 270). In the European Union, medicinal products that apply to Directive 2001/83/EEC will qualify (if applicable) for an environmental risk assessment before entering the market place in the Union.

4.3 United States

In the United States, the National Environmental Policy Act of 1969 (NEPA) requires all federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analysis. The NEPA process is intended to assist public officials to make decisions that are based on the understanding of environmental impacts, and to take actions that protect, restore, and enhance the environment (Olejniczak and Spindler, 200; 270). Hence, the United States Food and Drug Administration is required under NEPA to consider the environmental impacts of approving drugs and biologics applications as part of its regulatory process, as well as estimating the expected introduction concentration of an active moiety into the aquatic environment. Selected product types are given in the "Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications" (Food and Drug Administration, 1998).

More recently, there have been discussions that the US Environmental Protection Agency (EPA) has listed some pharmaceuticals as candidates for regulation in drinking water as well as launching a survey to check for scores of drugs at water treatment plants across the nation. The EPA's new study will look for 200 chemicals and microbial contaminants, which include 125 pharmaceuticals, at 50 plants that treat drinking water (Donn, 2009). The research will determine if regulations are needed. As the first step towards the possible drinking water standards, the EPA has put 13 pharmaceuticals on the Contaminant Candidate List under the Safe Drinking Water Act, which includes sex hormones as well as the antibiotic erythromycin, among others. No pharmaceutical has ever reached the Contaminant Candidate List in the 12-year history, but medicines now make up 13 percent of the target chemicals on the latest list "based on their potential adverse health effects and potential for occurrence in public water system." However, EPA officials have acknowledged that no chemical on the list has ever been made subject to a national water quality standard (Donn; 2009).

While European Union nations and the United States have initiated investigations into the risks of PPCPs in the aquatic environment, there has been comparatively fewer research projects conducted in Canada. The European Union started to list these chemicals in the late 1970s and since the mid-1980s it has been compulsory to set up an environmental risks assessment for all new chemicals (Kummerer, 2004; VII). However, in Canada, inconclusive evidence of fate and effects to humans and wildlife may have delayed the government's response to regulate PPCPs in the environment. Canada is relatively new to the practice of conducting risk assessments for PPCPs. As previously mentioned, Environment Canada and Health Canada are at the beginning of a regulatory process that will permit the assessment of medicinal products regulated under the Food and Drug Administration with respect to their potential effects on the environment (Olejniczak and Spindler, 200; 270).

In essence, there is no major economy that constrains the human use of PPCPs or biologics. PPCPs play an important role for human health and a market demand for such products exists. There are clear legislative limitations to deny humans the access to these products. PPCPs are simply an unmanaged set of environmental emissions. The following section will assess and evaluate a management framework for collecting and disposing of leftover residential drugs.

5. Management Framework – Take-Back Program

Based on the aforementioned understanding of the aquatic effects of PPCPs, there are reasons to be concerned about the continuous exposure to certain compounds, such as EE_2. The primary paths for PPCPs and their metabolites entering waterways from households are through excretion after use or disposal before use, either down the toilet into sewers and septic systems or into household garbage (Figure V). When people take medication, only a fraction is completely absorbed by the body, and the excess is excreted as unchanged compounds or processed metabolites (Kotchen, et al., 2009; 1476). In municipal sewage, the compounds make their way to wastewater treatment facilities that are not equipped to degrade medicinal substances and in septic systems, the compounds leach directly into ground water. Disposal in household garbage will end

up in landfills with the potential to eventually enter waterways through leachate (Kotchen et al, 2009; 1476). A wide variety of pharmaceutical compounds have been detected in landfill leachate, albeit at low levels, from lined landfills and in groundwater down-gradient of unlined landfills (Hubbard, 2007; 15).

It is not known exactly what percentage of pharmaceutical compounds in waterways originates from direct disposal versus excretion or whether disposal contributes significantly to the overall quantities of pharmaceutical compounds in the environment. By most estimates, disposal is considered to contribute to less than 15 percent of pharmaceuticals in municipal wastewater (Metcalfe, N/A; 14). Despite these clear data gaps, it has been argued that the quantities alone are not the only concerns with respect to their potential environmental impact. Also of importance would be any temporal or spatial characteristic of their release, which differs from the continual but low-level releases resulting from excretion (Ruhoy and Daughton, 2007; 22). Disposal holds the potential to introduce transiently high quantities of active pharmaceutical ingredients into sewage (presumably from industries) and these spikes in concentrations could lead to increased exposure for aquatic organisms, for example, should the active pharmaceutical agent survive wastewater treatment; risks could also be increased with respect to the homeostasis of the unique assemblages of microbial consortia that exist at each activated sludge wastewater treatment facility (Ruhoy and Daughton, 2007; 22).

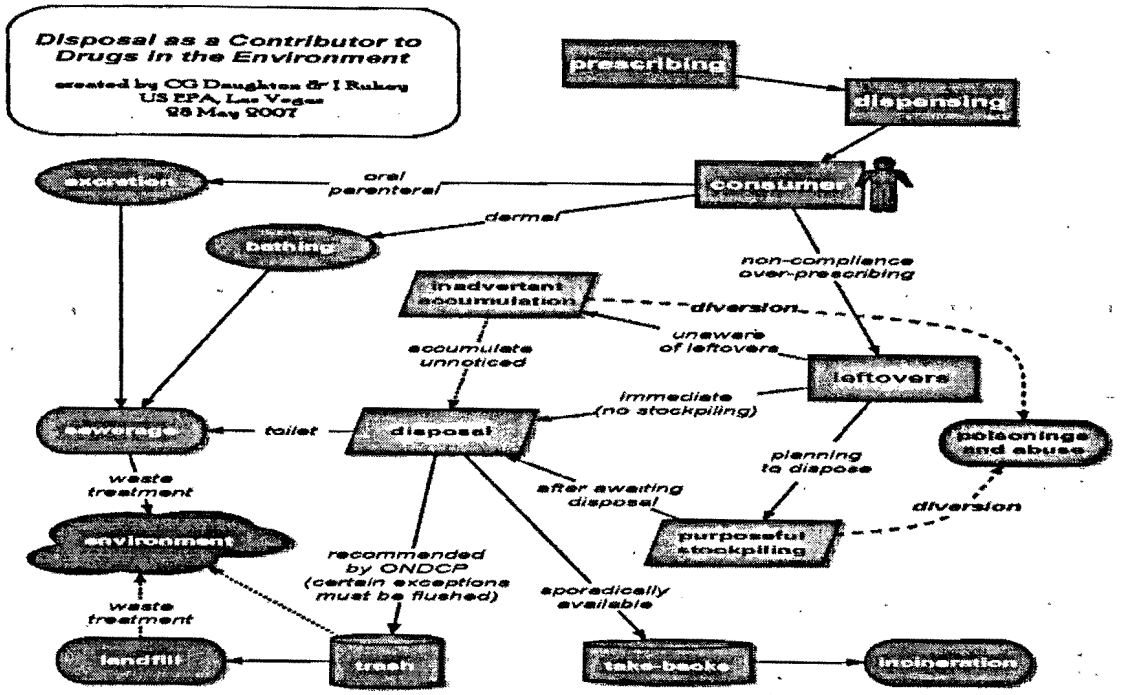

Figure V. Role of leftover drugs in the exposures of humans and the environment (Ruhoy and Daughton, 2007)

A take-back program is a management option that manages pharmaceuticals from entering the wastewater stream or the landfills in the first place. It provides a means for consumers to safely and efficiently dispose of unused/expired drugs. A key driver in a take-back program is to collect, manage and dispose of pharmaceuticals (most of the programs use hazardous waste incineration with emissions controls) and reduce environmental impact. A take-back program designed to minimize the introduction of pharmaceutical residues to the environment is considered particularly advantageous for dealing with the foreseeable increase and expansion in drug use (e.g., as the population ages, new therapies continue to be developed, etc.) (Daughton, 2007; 25). Such programs also offer collateral social benefits such as decreasing accidental poisonings and reducing drug abuse. In Canada, most provinces have some form of voluntary disposal program for pharmaceuticals, including Alberta, Nova Scotia, Prince Edward Island, Saskatchewan, Manitoba and Newfoundland. Most of the programs are either funded by industry or government, or a combination of both (Gagnon, Edith, 2008; 11).

Statistics for Canada reveal the methods of disposing of unused/expired drugs include the following (before take-back programs were implemented):

- 46 percent had disposed of their unwanted medications into the toilet;
- 31 percent disposed them to trash;
- 17 percent had already been taking them back to the pharmacy;
- 2 percent returned theirs to their physician; and
- 4 percent used other routes (Daughton, 2003; 783).

Similar results were recorded in the United States where the majority of consumers were either flushing unused/expired medications down the toilet or disposing them in household garbage. Of those surveyed:

- 54 percent disposed of medications in the garbage;
- 35.4 percent flushed medications down the toilet or sink;
- 7.2 percent did not dispose of medications;
- 1.4 percent returned medications to a pharmacy; and
- 2 percent said that they used all medications before expiration (Daughton, 2003; 781).

These statistics further reinforce the need for effective, efficient and economical take-back programs for unused/expired pharmaceuticals. In Ontario, 224 million units (defined as a bottle, tub or package) of pharmaceuticals entered the Ontario market in 2007 and weighed 6,589 tonnes (including packaging) (PCPSA News Bulletin, August 2009; 2). According to the Pharmaceutical Working Group, approximately 10 percent of pharmaceuticals introduced to the market are not consumed, and therefore theoretically available for collection. This study focuses on the disposal of medications via sewers or household trash as an entry pathway to the environment, rather than the release via

excretion, given the first route is voluntary and amenable to modification by programs such as take-back, and the latter route is involuntary.

5.1 Overview of British Columbia's Medications Return Program

One of the longest running pharmaceutical take-back programs is the one in British Columbia. British Columbia's Medications Return Program is a mandatory recovery program that has been operating for over a decade. A number of jurisdictions, including Oregon have touted British Columbia's Medications Return Program as a successful, model take-back program (Hubbard, 2007; 2). British Columbia's program, like many others of its kind, manages waste at the end-of-life stage thereby reducing its environmental impact. The Medications Return Program was designed to accept the free return of all household (not hospital) prescription drugs, over-the-counter medications, natural health products and vitamin supplements (not accepted are sharps, needles, contact lens disinfectant, shampoos, cosmetics, etc.) as defined under the federal Food and Drugs Act.

It was established voluntarily by British Columbia's pharmaceutical industry (as founded under EnviRx program) in November 1996. In March 27, 1997, through the Post-Consumer Residual Stewardship Program Regulation, it became mandatory for the producers and consumers of various products, including pharmaceuticals, to take responsibility for the management of their leftover medication. The regulation came at the request of the pharmaceutical industry as a way of ensuring consistent objectives and a level playing field for all producers through universal participation in the program (PCPSA, July 2009). The Post-Consumer Residual Stewardship Program Regulation was subsequently repealed in 2004, and the key provisions were incorporated into the schedule of the Recycling Regulation (B.C. Reg. 449/04), under the Environmental Management Act.

In the Recycling Regulation, the pharmaceutical product category is prescribed under the Residual Product Categories in Schedule 2. The Recycling Regulation gets its authority from the Environmental Management Act and is administered by the British Columbia's Ministry of Environment. The pharmacy is responsible for the safekeeping of

the Medications Return Program container and its contents while on their premises. Once the container is full, the pharmacist contacts the Program Administrator who arranges for pick up by a licensed hauler and replacement of containers within seven days. The wastes are than incinerated, which is an accepted best management practice for managing residual medications collected. The program is an adaptation of British Columbia's EPR program.

5.1.1 Extended Producer Responsibility

While the EPR principle has a variety of meanings to different policy-makers, the common thread of all EPR programs is that they aim to improve environmental performance of producers by having them take life-cycle responsibility for their products. In British Columbia, ERP is an industry-led product stewardship program that manages the end-of-life of products in order to improve waste management. It also shifts responsibility away from government and taxpayers and towards producers. British Columbia defines EPR as a "principle of the user pay, whereby responsibility for managing materials and products in the waste stream is borne by producers and consumers rather than the general taxpayer" (PCPSA, Program Plan, 2006; 3). British Columbia's Ministry of Environment considers the four following principles for an EPR program, developed by the Industry Product Stewardship Business Plan:

1) **Producer/User Responsibility** where responsibility for waste management is shifted away from taxpayers to producers and users;

2) **A Level Playing Field** where all brand-owners are subject to the same stewardship responsibilities and all consumers have reasonable access to product collection facilities;

3) **Results-Based** programs that focus on results and that provide brand-owners with the flexibility to determine the most cost-effective means of achieving the desired outcomes with minimum government involvement; and

4) **Transparency and Accountability** where program development is open.

British Columbia aligns its goals and principles of an effective EPR with the CCME. CCME set the national policy direction by releasing in October 29, 2009, the Canada-Wide Action Plan for Extended Producer Responsibility. CCME offers a framework for an EPR program, strategies, performance measures and targets to ensure a harmonized approach. The overarching goals of CCME's principles are "to minimize environmental impacts, maximize environmental benefits, promote the transfer of end-of-life responsibility for the product to the producer and encourage design for environment" (CCME; June 2007; 2). CCME's principles are based on principles originally proposed by the OECD, which Canada is an active partner. There are a number of benefits in taking an approach where the producers play a larger role in managing their own waste. Aside from reducing financial and physical burdens upon government, the involvement of the private sector tends to increase the efficiency of waste management practices, such as better logistics from transportation (Rossem et al., 2006; 4).

5.2 Approach and Methodology

This study reviewed British Columbia's approach to waste management of unused/unwanted household pharmaceutical products from a legislative/regulatory and policy/program implementation perspective. Given the length of time that the program has been in existence, it can provide some key evidence as to whether its approach to recovery has been effective, efficient and economical. This study will examine whether the design of British Columbia's take-back program has been effective in controlling the disposal of unused/expired drugs and thereby reducing the overall loadings to the environment. In addition, this study will determine whether the program was justifiable based on the current results achieved.

The approach to the study will be to:

1) Investigate EPR programs in other jurisdictions and the results achieved. Two different pharmaceutical take-back programs will be explored including Alberta and Maine. In addition, two related consumer recovery programs, other than

pharmaceuticals, will be examined including California's used oil recovery program and Ontario's waste diversion program.

2) Conduct a comprehensive assessment of British Columbia's Medications Return Program in terms of its legislative/regulatory and program objectives; the type of policy instrument used to implement the program; and the results achieved.

3) Finally, British Columbia's Medications Return Program will be evaluated based on CCME's environmental principles for design and development of EPR policies and programs. CCME developed some common principles for stewardship programs through their Canada-wide Action Plan for EPR. Since these are the standards that provinces should ultimately strive towards, it was critical to assess British Columbia's Medications Return Program against these principles. The lessons learned from other jurisdictions will be highlighted where possible.

Since no single program delivers complete success, there are merits to explore other jurisdictions' EPR programs based on similarities and differences, and reflecting on the range of approaches (Table VI). Alberta's ENVIRx Pharmaceutical Stewardship Program is considered a good comparator since it is operationally a similar program to British Columbia and has achieved a high level of success. Maine's Unused Disposal Pharmaceutical Program was explored primarily because it is one of the few take-back programs that includes regulatory requirements as well as being innovative in practice. In further examining take-back programs, California's Used Oil Recovery program provided an opportunity to examine a different consumer product recovery program that employed another type of policy instrument, economic incentives. Ontario's Waste Diversion program, and more specifically the Deposit Return Program for beverage alcohol containers, was selected as a comparator since it is also a consumable product.

	Year of Establishment	Mandatory or Voluntary	Policy Instrument
British Columbia's Medications Return Program	1996	Mandatory	Regulatory
Alberta's ENVIRx Pharmaceutical Stewardship Program	1988	Voluntary	Voluntary
Maine's Unused Pharmaceutical Disposal Program	2003	Mandatory	Regulatory
California's Used Oil Return Program	1992	Mandatory	Economic
Ontario's Waste Diversion Act	2002	Mandatory	Economic

Table VI. Jurisdictional stewardship programs

The information for this study was derived from scientific journals, technical reports, a stakeholder report, federal and provincial legislation/regulations, and the author's experience with related management of program operation. In addition, written inquiries were directed to the relevant provincial agency.

5.3 Analysis

5.3.1 Alberta's ENVIRx Pharmaceutical Stewardship Program

Objective

Alberta's ENVIRx program is a take-back program, where consumers drop-off unused/expired medications to participating pharmacies for collection and disposal. It is

a province-wide voluntary program established in 1988 by the Alberta Pharmaceutical Association. In 2001, the management of the program changed from the Alberta College of Pharmacists to the Pharmacists Association of Alberta, now known as the Alberta Pharmacists' Association (RxA). Various pharmaceutical companies (i.e. the Canadian Generic Pharmaceutical Association, Rx & D, NDMAC (Non-prescription Drug Manufacturers Association of Canada) – Advancing Self-Care and small grants from Alberta's government fund the program. The main drivers of the program are: lowering health care costs, reducing medication from the municipal waste stream, and protecting the environment from improper disposal practices. There are no product-specific fees associated with the operation of the program.

Since ENVIRx is voluntary, it is not supported by a formal regulatory framework. Representatives from the pharmaceutical associations sit on the ENVIRx Advisory Committee and provide oversight to the program. The RxA manages the program, secures funding and solicits stakeholders to participate in the program as well as regularly reviewing the program to ensure it operates effectively and efficiently. An annual report, including the annual collection statistics, is produced; however, this is not publicly available (Environment Canada, March 2007). There are no collection targets in place for the program. Detailed information on program revenue and expenses is unavailable. Since the transfer of the program to the RxA, efforts have been made to increase and secure long term funding so the program can be sustained (Environment Canada, March 2007).

Results

There are approximately 800 participating community pharmacy locations across Alberta (Environment Canada, March 2007). From 1988 to 2005, the program collected and disposed of 520 tonnes of unused/expired medications. In 2004, the program collected 32 tonnes of waste medication and in 2005, 37 tonnes were collected (Environment Canada, March 2007). The average rate of returns per capita for the province was 0.01 kg/capita (Health Canada, November 2008).

5.3.2 Maine's Unused Pharmaceutical Disposal Program

Objective

The State of Maine is the first state in the United States to pass legislation for the management of unused/expired medications. In 2003, Maine passed Public Law 2003, Chapter 679, which created the Unused Pharmaceutical Disposal Program with the purpose of ensuring the safe and proper disposal of medications. The program is administered by the Maine Drug Enforcement Agency. Some key drivers of Maine's program are: to reduce unintentional poisonings of children, the abuse of pharmaceuticals by teenagers, the accumulation of medicine in the homes, and the potential deleterious effects on wildlife and humans due to drug accumulation in waterways (Illinois-Indiana Sea Grant 2.0, 2009; 42).

Under this system, consumers use prepaid mailing envelopes to send their unwanted pharmaceuticals to the Maine Drug Enforcement Agency. The envelopes are to be made available to the public at various locations including pharmacies, physicians' offices, and post offices (Illinois-Indiana Sea Grant 2.0, 2009; 42). Once the envelopes are received by the agency with the unused/expired medications, they are catalogued and destroyed. The program has been implemented in 2 phases. Phase 1 focuses on 4 counties, the participation of people 65 and older with limited press/marketing and no public education. The intent of Phase 1 is to monitor the program and pilot the protocols. Phase 2 will involve state-wide implementation and incorporate the lessons learned in Phase 1 (Kaye, 2009).

Results

Data were collected for Phase 1 and analysed in August 2008. Data was collected primarily from surveying the participants that returned the drugs in the envelope and project pharmacists cataloguing the returned drugs. Ninety percent of returns were prescription drugs and 10 percent were over the counter. Some interesting findings included: many of the mailers contained full bottles of unused drugs from mail-order pharmacies or pharmacy services; received full bottles of very costly antiretroviral drugs (HIV/AIDS drugs); and older medications were not uncommon (some returns were

noted to be as many as 7 years old) (Kaye, 2009). The survey data from Phase 1 indicated the following:

- average age of program participants were 70 years old;
- top reasons for accumulation included death of a relative or loved one, medicine expired or doctor told the patient to stop taking the medicine;
- 15 percent of respondents did not know what kind of medicine they were returning;
- 57 percent were returning medicine for themselves; and
- 53 percent were returning medicine for a relative (Kaye, 2009).

Based on the same surveys, the top reason for using the program was that it was best for the environment (83 percent), and the safety of themselves and their families (8 percent).

The next step (Phase 2) is that the program goes state-wide. Pharmacies would be the primary point of distribution for program envelopes as well as home health, doctor offices, social service programs and area agencies on aging. There will be extensive press/marketing and public education of the program as it expands to other age groups. There would be 7,200 mailers available through state-wide network of participating pharmacies and partnering sites (Kaye, 2009).

5.3.3 California's Used Oil Return Program

Objective

California's Used Oil Program was established to reduce the illegal disposal of used oil that may contaminate water supplies, and promote the reuse. Under the mandate of California Oil Recycling Enhancement Act, the state's Integrated Waste Management Board created the Used Oil Program. The statute called for the establishment of local collection programs that encourage the recycling of used oil to be achieved largely through the award of annual block grants to local governments. Block grants are sums

of money awarded with only general provisions as to how they must be spent (Conn, 2009; 3).

Oil manufacturers are required to pay the California Integrated Waste Management Board 16 cents for every gallon of lubricating oil sold, transferred, or imported for use in California. The revenues are used to make annual block grant awards to local jurisdictions; pay a recycling incentive of no less than 16 cents per gallon to members of the public and others for the collection and recycling of used lubricating oil; establish an annual reserve, to pay for Board administration of the program, and to pay for the reporting and inspection of used oil haulers and facilities by the Department of Toxic Substances Control; and provide appropriations for state-wide outreach, competitive grants, and other purposes (Conn, 2009; 7). The program requires that certified used oil collection centres be established and be required to pay a recycling incentive of 16 cents per gallon to any person who brings in used lubricating oil.

Results

Since 1993, over 600 million gallons (estimated) of used lubricating oil have been recycled and reclaimed. In 2004, the number of certified used oil collection centres had stabilized at around 2,600. In fiscal year 2000-01, roughly $3 million was awarded in non-profit grants (non-profit organizations for used oil and used oil filter recycling projects); in 2001-02, $5 million in opportunity grants (provide additional funding to local governments to expand oil collection and outreach/education programs); and in 2002-03, $4 million in non-profit and research, testing and demonstration grants (Conn, 2009; 10).

California's Integrated Waste Management Branch's report suggests that the do-it-yourselfer (DIY) sector, as a proportion of all California households, probably decreased during the program's existence, reaching about 17.6 percent by 2001 and the total amount of used oil returned by DIYers for recycling remained steady. This is significant because of the assumption that DIYers are the people most likely to dispose of used oil illegally (Conn, 2009; 14).

5.3.4 Ontario's Waste Diversion Act

Objective

In June 2002, Ontario's Waste Diversion Act was passed. The purpose is to promote reduction, reuse and recycling of waste and to facilitate the development and implementation of waste diversion programs. It requires all companies that introduce packaging and printed paper into Ontario's consumer marketplace to share in paying 50 percent of the funding of Ontario's municipal Blue Box waste diversion programs. Stewardship Ontario is the industry funding organization developed to meet the requirements of the Waste Diversion Act, and it launched its program in February 2004. Stewardship Ontario is a multi-stakeholder body that acts as a connection between government and industry as the funding organization responsible for setting, financing and implementing a plan to meet the provincial waste diversion requirements as set out in the Waste Diversion Act (Five Winds Environment, 2006; 6).

Part of Stewardship Ontario's policy is to change industry behaviour. Stewardship Ontario recognizes its current structure does not provide incentives for producers to redesign their packaging for better environmental performance, a program known as Design for Environment. It has therefore planned to step up incentives for change through increased separation of material groups and assigning variable fees according to predetermined formulae (Five Winds Environment; 2006; 6).

In 2006, Premier McGuinty announced a new deposit return recycling program for beverage alcohol containers. The primary target of the program is to divert an additional 25,000 to 30,000 tonnes from landfill (historically collected through the Blue Box system) and, by freeing up space in blue boxes. The program is designed to achieve the following environmental goals by the end of the contract term: 85 percent combined recovery rate for containers that are part of the program; no recyclable glass materials going to landfill; and 90 percent of recovered glass being recycled into high value products (The Beer Store, 2009; 23).

Results

The Ontario Deposit Return Program was launched on February 5, 2007. Consumers pay a deposit of 10 to 20 cents depending on the size of the container. Empty beverage alcohol containers can be returned to any of 784 locations across the province including the Beer Store outlets, Liquor Control Board of Ontario agency stores, The Beer Store's Retail Partners and contracted empty bottle dealers (The Beer Store, 2009; 23).

In its second full year of operation, there was an increase in the collective (combined) recovery rate from 2008 of almost 6 percentage points; from 67 percent in 2008 to 73 percent in 2009. Most categories and sizes of container returns experienced a growth of about 5 percent recovery from the previous year, with the small glass container recovery rate improving by 7 percentage points; from 56 percent in 2008 to 63 percent in 2009. Small tetra and bag-in-the-box containers were the only container types to experience a decline in total recovery rate, declining by 9 percentage points (The Beer Store, 2009; 26).

In addition, the Beer Store has made tangible efforts in Design for the Environment. In order to improve the efficiencies of the refillable bottle system the Canadian brewing industry has adopted the use of a standardized refillable beer bottle which significantly reduces the cost of sorting proprietary or brewer specific refillable bottles as well as eliminating the need for brewers to perform costly packing line changeovers to switch from one bottle type to another (The Beer Store, 2009; 4).

5.3.5 British Columbia's Medications Return Program

Objective

British Columbia's Recycling Regulation provides the legal framework for establishing industry-led product stewardship programs. With respect to pharmaceuticals, it requires the product producers (e.g. product manufacturer, distributor or brand-owner) of pharmaceutical products to be responsible for the management of their post-consumer wastes by providing the public with a way to dispose unused/expired products in an environmentally sound manner. Producers or their agency must develop a business plan called a Product Stewardship Plan that proposes goals and targets and submit it to

the Ministry of Environment for review and approval. All producers are required to have and comply with an approved Product Stewardship Plan or be part of a recognized pharmaceutical stewardship program and producers are informed that failure to so contravenes legal requirements.

British Columbia's Recycling Regulation is open and non-prescriptive. Since it is a performance-based regulation, the focus is on the environmental outcome where the pharmaceutical industry is free to set its own targets and achieve its goals in whatever fashion they like. It provides flexibility in planning and implementation of the program and recognizes the notion that one size does not fit all. The policy approach used to implement the EPR program incorporates regulatory and informational instruments. It is a regulatory requirement to have the following: an EPR scheme for designated product categories, a process whereby product producers establish targets and report on performance, as well as penalties to be imposed for non-compliance with EPR program. In addition to regulatory requirements, the EPR program uses public information as a tool to implement the program. This includes education to promote community awareness about how to dispose of products.

Part 1 of the Recycling Regulation enables an industry-established stewardship organization to carry out its duties on behalf of each member. The Canadian Generic Pharmaceutical Association, Canada's Research-Based Pharmaceutical Companies (Rx&D group) and NDMAC - Advancing Canadian self-care represent the majority of the brand-owners of pharmaceuticals and self-care health products (PCPSA, July 2009). These groups created the Post-Consumer Pharmaceuticals Stewardship Association (PCPSA). PCPSA is an independent, not-for-profit industry-sponsored association created in 1999 to coordinate the program in response to a request from the British Columbia Minister of Environment. It acts on behalf of the pharmaceutical industry to administer the approved Program Plan under the Recycling Regulation.

The Pharmaceutical Residual Management Group Ltd. has been contracted by PCPSA to manage the program's daily operations. It is responsible for activities including maintaining a database on participating community pharmacies, communication of program requirements to enrolled pharmacies, collection of unused/expired medications

from pharmacies, storage of collected containers, shipment and disposal of containers and ensuring all necessary environmental permits and insurances are current (PCPSA, Program Plan, 2006; 9). The Program Plan provides the pharmaceutical industry with a collective means of adhering to the requirements of the regulation and a cost-effective and efficient way to meet their obligations under the Recycling Regulation (Ministry of Environment, Recycling Regulation Guide 2006; 5). The program costs become an internalized cost for the pharmaceutical industry. For 2007, the program revenue, which is created from the contribution of individual companies, was $325,000 and expenses were $294,000. For 2006, program revenue was $253,000, and expenses were $256,000 (Gardner Pinfold Consulting 2008; 43). Annual costs to drug producers ranged from $200 to $15,000; most producers paid $6,000 to $7,000 per year (PCPSA program update, 2007).

Part 2 of the Recycling Regulation outlines the elements of the Product Stewardship Plans. The regulation requires that producers establish conditions including, among others, performance standards and targets for evaluation and accountability purposes, provisions for consumer access and awareness, consultation during the plan development, and efforts taken to measure and reduce environmental impacts throughout the lifecycle of a product. Producers are given flexibility to determine the most cost-effective means of meeting these outcomes. In addition, producers are required to correctly inform the retailers about the program and retailers are required (section 11) under the Recycling Regulation to provide consumer information. Every five years, the producer must review the approved plan and submit any amendments (Ministry of Environment, Recycling Regulation Guide 2006; 6).

PCPSA's Stewardship Plan articulates how it intends to achieve its priorities (for the period 2007 to 2011) with respect to performance measures, funding the costs of collecting the products, having accessible collection facilities and making the consumers aware of the product stewardship program.

PCPSA elected not to use recovery rates as a measurement of success. In lieu of recovery rates, the method for evaluating success of the program has been based on the following five targets and performance measures:

1. Waste composition studies:

The purpose is to conduct waste composition studies, which are studies analyzing the household waste stream, and as more unused/expired pharmaceuticals are collected through the Medications Return Program, significantly less should appear in waste collection. However, the waste composition studies should be statistically significant to establish the presence of pharmaceuticals within the household waste category. For instance, the standard deviation is 0.5 and if the pharmaceutical quantities are smaller (e.g., 0.3), since the deviation is higher than what is found and based on extrapolation (indicating that 0.3 is equal to 40 metric tonnes), the amount is deemed to be statistically insignificant (PCPSA, 2009).

Target (until 2011) - decrease the presence of pharmaceuticals in Regional Districts that conduct waste composition studies.

Performance measure – report amounts of pharmaceuticals estimated in statistically significant Regional District's waste composition studies.

2. Number of collection points:

The goal is to provide a convenient system for the collection and disposal of unused/expired medications and ensuring both the public is provided with information on locations and the pharmacies are informed about their role in the Medications Return Program.

Target (until 2011) – maintain a pharmacy program participation rate of 90 percent.

Performance measure – report percentage of participating pharmacies yearly.

The strategies that have been established include contacting new licensed community pharmacies from an amended list purchased from the College of Pharmacists on a monthly basis; contact existing pharmacies with ownership and/or manager changes on a quarterly basis; and contacting pharmacies with a significant change in collection patterns.

3. Public awareness:

The goal is to ensure citizens are informed of the Medications Return Program and are provided with current information regarding the availability of a system for the collection of unused/expired medications.

Target (for 2011) – 50 percent increase in public awareness of the Medications Return Program compared to 2007.

Performance measures – establishing a public awareness level based on a public survey in 2007; and measure changes in awareness and behaviour through a survey in 2010.

The strategies that have been set to achieve this goal include:

Year 1 – establish a level for public awareness of similar recovery programs; set performance targets for awareness and behaviour; promote program by advertising in 2 Regional District's recycling calendars, website and 4 special events;

Year 2 to 3 - increase publicity in another 2 Regional District annual calendars and continue to support special events; and

Year 4 – measure awareness and usage of program with a public survey.

4. Quantity of pharmaceutical products collected:

The goal is to ensure that all participating community pharmacies take advantage of the program. The quantity is measured in absolute weight of medications returned by the public to pharmacies.

Target (until 2011) – maintain a minimum quantity collected of 14,000 kg.

Performance measure – report total quantity collected on a yearly basis with quarterly results by Regional Districts.

The strategies that have been set include:

Year 1 – promote program at special events (e.g. Pharmacy Awareness week, stakeholder initiatives, etc.);

Year 2 – continue to work with members and participating pharmacies to organize special collection events and publicize the program;

Years 3 to 4 – continue to work with members and community pharmacies with special collection events and retailers; and

Year 5 – to be developed based on public survey results in year 4.

5. Promotion:

Target (until 2011) – generate publicity on the Medications Return Program in 14 Regional Districts or municipalities' websites with recycling sections. Notification of the program in 13 annual recycling calendars.

Performance measure – increase in awareness of program.

The strategies set to achieve this include:

Year 1 to 2 – contact all 28 Regional Districts with promotional material and key messages for their websites;

Year 3 – follow up on advertising on Regional Districts/municipalities websites and annual calendars;

Year 4 – evaluate the outcome of the promotional program through a public survey.

The Recycling Regulation requires the producers to determine how to fund and manage their program. PCPSA provides funding for the collection, transportation, storage, promotional activities and disposal of the unused/expired pharmaceutical products. The program is funded through fees remitted by producers once a year. It is shared between the brand name (45 percent) generic (35 percent) and self-care health products (20 percent) industries (PCPSA, Public consultation meeting; 1). The contributions are based on prescriptions dispensed in British Columbia during the previous year and/or at a per unit rate of the sale of self-care health products (PCPSA, Program Plan 2006; 9). Rates are set yearly by the Board of Directors in relation to the projected costs. No fees are passed along to the public at the time of purchase or at the point of collection and

pharmacies can sign up voluntarily (no fees charged) to be a collection point for the program (PSPSA 2008, 6). Yearly reviews are taken to identify new brand-owners and the names are obtained from Health Canada, which has a directory for all drugs sold in Canada.

The Recycling Regulation requires making consumers aware of collection facilities. There are a number of ways that the public is educated about collection facilities, which include messages at/from community pharmacies, as well as the general Medications Return Program. These include organized media campaigns, coverage in the local news/talk shows/television, print media (brochures, poster distribution, mailouts, news bulletin, municipal garbage/recycling calendars, newspaper), website, health awareness events, environmental trade shows, a toll-free recycling information hotline and an ambassador program (PCPSA, Program Plan 2006; 11).

An Annual Report outlining how the yearly objectives were met as a way of monitoring progress against performance expectations. The Annual Report needs to be submitted to the Director of Waste Management, Environmental Quality Branch of the Ministry of Environment, on or before July 1 each year documenting the performance in relation to the plan.

It is necessary for new producer-led programs to hold broad multi-stakeholder consultation on all aspects of the proposed program. PCPSA conducted public consultation meetings to address possible concerns with its Medications Return Program. However, the circumstances surrounding the consultation process, including who participated in this process (e.g. non-governmental organizations) were not made available.

The Recycling Regulation requires producers to disclose the efforts taken to measure and reduce environmental impacts throughout the lifecycle of a product. In regard to measuring the environmental impacts of pharmaceutical products entering the environment, PCPSA is of the position that these matters are already being dealt with at the federal level under the CEPA, it has been recommended that the need to consider environmental impact throughout the product's life-cycle be excluded from the Program

Plan. The rationale provided is that Environment and Health Canada already assess the environmental and human safety impact of pharmaceuticals entering the environment through the NSNR (discussed in the previous section). The Existing Substances Division conducts work jointly with Environment Canada, the department responsible for assessing risk to existing substances to the environment, to investigate whether a substance is "toxic" as defined in the Act and reviewing options for controlling risks to human health and/or the environment (PCPSA, Program Plan 2006; 12).

In addition, due to a manufacturer's limited ability to reduce the environmental impact of these products without affecting their legislative/regulatory obligations under the Food and Drugs Act, it was decided that this component would not be further explored by PCPSA (PCPSA, Program Plan 2006; 12).

The Recycling Regulation requires producers to disclose the efforts taken to consider the pollution prevention hierarchy, as outlined below. This section requires the producers to demonstrate any efforts to improve environmental performance throughout a product's lifecycle including: a) reducing the environmental impact of producing the product by eliminating toxic components and increasing energy and resource efficiency b) redesigning the product to improve reusability or recyclability c) eliminating or reducing the generation of unused portions of a product that is consumable d) reusing e) recycling the product f) recovering material or energy from the product, or g) otherwise disposing of the waste from the product in compliance with the Environmental Management Act. PCPSA asserts this section is not feasible in this category of a consumable product, since the safety, efficacy and quality can affected.

Results

Based on the most recent submission of PCPSA's Annual Report, January 2008 to December 2008, the following results were achieved:

Quantity Collected. Recovery rates (measurement of what is collected as a proportion of what is sold) are not used to measure program success because there are limitations in reporting the recovery rate. Medications may have a long period between purchase and return and prescription drugs dispensed should be fully consumed unless otherwise

directed by a health professional. In place of using recovery rates, the absolute collection of medication in kilograms (mass recovered) was recorded. The average rate of returns per capita for the province was 0.008 kg/capita. Collection across the province has increased by 50 percent, from 23,384 kg in 2007 to 35,704 kg in 2008 (PCPSA, Annual Report 2009, 11) (see Table VII).

Pre or post - Regulation	Year	Absolute Collection (kg) and per capita/weight	Percentage Change from previous year	Retail Outlets	Cost of Program (where available)
Pre-Regulation (program established November 1996)	1996 (November) - 1998 (April)	6,703 kg†			
Post-Consumer Residual Stewardship Program Regulation (March 1997)	1998 (May) – 1999 (April)	10,104 kg†	51% increase		
	1999 (April) – 2000 (March)	11,479 kg†	14% increase	650	
	2000 (April) – 2000 (December)	4,490 kg†	60% decrease	550	
Program re-launch as Medications Return Program	2001 (January - December)	10,500 kg or 0.002/capita	134% increase	680 (representing over 90% of licensed pharmacies)	
	2002 (January - December)	18,881 kg or 0.004/capita (Note: higher collection weight due to collection of old pails from the pharmacies in the 4th quarter)	80% increase	719 (representing over 86% of licensed pharmacies)	
	2003 (January - December)	10,094 kg or 0.002/capita (Note: all pharmacies started 2003 with empty containers and consequently below a normal yearly amount)	47% decrease	734 (representing over 86% of licensed pharmacies)	
Recycling Regulation (2004)	2004 (January - December)	15,503 kg or 0.003/capita	54% increase	802 (representing over 90% of licensed	$195,600

Pre or post - Regulation	Year	Absolute Collection (kg) and per capita/weight	Percentage Change from previous year	Retail Outlets	Cost of Program (where available)
				pharmacies)	
	2005 (January – December)	18,012 kg or 0.004/capita	16% increase	Representing 80% of licensed pharmacies	$225,000
	2006 (January – December)	19,995 kg or 0.004/capita	11% increase	889 (representing 92% of licensed pharmacies)	$257,000
	2007 (January – December)	23,875 kg or 0.005/capita	19% increase	915 (representing 93% of licensed pharmacies)	
	2008 (January - December)	35,704 kg or 0.008/capita	50% increase	942 (representing 95% of licensed pharmacies	$315,000
	2009 (year-to-date – August 2009)	23,989 kg	TBD		

† per capita/weight not calculated due to inconsistency of months recorded

Table VII. Absolute collection quantities annually

Number of collection points (community pharmacies). The participation of a pharmacist is central to the success of the program. In 2008, there was an increase in pharmacy participation rates from 93.3 percent to 95 percent with accessibility to over 942 pharmacies (PCPSA, Annual Report 2008, 3). PCPSA has the most extensive network of the entire EPR program in British Columbia (PCPSA, Annual Report, 2006; 3).

Public Awareness. Based on 2007 survey results, the target for 2008 was set for 35 percent (compared with baseline program awareness level at 31% SD ±4.3%). Efforts in the first year of PCPSA's new plan (2008) yielded a 53 percent increase in returned pharmaceuticals to a total weight of 35,704 kg or 0.008 kg/capita (Smirl, November 5, 2009).

Promotion. There was an increase in media coverage on safe disposal for waste medications: several talk shows featuring safe disposal of medications; health awareness events promoting the Medications Return Program; and information on the program was published with Annual Recycling Calendars, brochures, flyers and posters. The increased media coverage was in part a reaction to the ban of stewardship products from the regular waste stream in Metro Vancouver.

In addition, in order to ensure citizens were informed of the program, PCPSA contracted Recycling Council of British Columbia's "recycling hotline" service to provide information on medications disposal. The recycling hotline is a toll-free personal service that provides information on waste reduction, recycling, disposal and pollution prevention. Approximately 120 calls regarding medication disposal were received annually, representing less than 1 percent of their total calls. Similar to the hotline, a website is available for information on waste medications and safe disposal. There was a 65 percent increase in website use in 2008, compared to 2007.

Waste Composition Study. No reports were received in 2008.

5.4 Discussion

In this section, a number of critical issues raised in the previous section are discussed in greater detail in an effort to highlight whether British Columbia's Medications Return Program has been operating effectively, efficiently and economically. The results achieved through British Columbia's Medications Return program will be assessed by aligning with CCME's principles for an effective ERP program. Results achieved from different jurisdictions will be highlighted where applicable.

CCME principle – to the greatest extent possible, programs seek to reduce the environmental impact of a product.

One of British Columbia's Ministry of Environment's broader policy goals is to promote recycling of waste and other discarded consumer products in order to divert them from landfills and protect the environment and human health. Under the Recycling Regulation, the pharmaceutical industry, along with other ten industry groups, is

responsible for collecting and recycling leftover products that it manufactures by implementing and complying with their own product stewardship plans. The objective for these industry-led stewardship programs is to facilitate material recovery and reuse, supporting the secondary processing industry and eventually eliminating these reusable/recyclable materials from municipal landfills (Ministry of Environment, 2008; 2). Aside from pharmaceuticals, the other ten industry groups operating recycling programs include electronics, paint, oil, beverage containers, tires, pesticides, gasoline, solvents and flammable liquids, antifreeze and lead acid batteries.

British Columbia's government provides the flexibility for designing and implementing policy instruments that would promote environmentally sound waste management. Generally, there are four types of policy instruments that can be used including administrative (regulations), economic (incentives), direct government and voluntary (education/information). ERP programs that extend the producer responsibility to end-of-life management of their products normally include administrative, informative/education and economic policy instruments (Rossem et al., 2006; 3). In British Columbia, with respect to the pharmaceutical category, the policy mechanisms used to implement the EPR program are a combination of administrative and information/education. The administrative requirements include the obligation for producers to establish an infrastructure for collection/take-back of pharmaceutical products and reporting to authorities about the achievement of targets. The information/educational component include informing people about both the risks of improper disposal of pharmaceuticals along with the option of returning unused/expired medications to the pharmacy. Since the program does not use target recovery rates because medications are a consumable product, other targets are set by the producers such as public awareness levels. The success of the program largely depends on the consumers' level of awareness. Currently, approximately 31 percent of British Columbia residents are aware of the program, and only 24 percent of residents actually use the program (Gardner Pinfold Consulting, 2008; 41).

Compliance and enforcement are critical measures to ensure the regulation is effective. Currently, there are no issues of non-compliance with the associated regulation (Smirl,

November 5, 2009). The Recycling Regulation (section 16) outlines the offences related to the Act, with a stated maximum fine of $200,000. There are procedures in place to ensure compliance with the requirements of the Recycling Regulation. Non-compliance is defined as a lack of responsiveness from a brand-owner after more than two notices are sent from PCPSA outlining the producers' responsibilities. Exceptions can be made if the Board determines that the producer is not covered by the regulation (excluded products) or fees are paid by a third party (PCPSA letter to Director, 2007; 5). In the event that PCPSA does not receive a financial contribution from stewards within the prescribed time frame, PCPSA management utilizes the following notifications to underscore the importance of timely submission:

The first contact (60 days prior) – letter is sent to brand-owner obligated under the Recycling Regulation informing them of their responsibilities. PCPSA role is to advise any potential brand-owner and offer the approved Medications Return Program as a way to fulfill their regulatory requirements.

The second contact (30 days) – a second letter is sent to a brand-owner for lack of reply from the previous correspondence.

The third contact (30 days) – a final letter with a deadline for submitting membership documents and payments toward the plan is sent.

The fourth contact – a request for non-compliance actions is sent to the MOE with a copy to the brand-owner (PCPSA letter to Director, 2007; 5).

To date, this has been sufficient to convince producers to comply and the policy measures have worked to keep compliance at or close to 100 percent (Smirl, November 5, 2009). However, prosecution would be pursed if a producer chose to remain out of compliance after reasonable advice and warning.

British Columbia's industry led stewardship program is monitored, evaluated and continually enhanced by identifying other priority products to add to the Recycling Regulation. Currently, the government is intending to add mercury-containing products such as light bulbs and thermostats to the Recycling Regulation, as well as expanding

the existing list of recyclable electronic products (i.e. stereos, cell phones and other hand-held devices) (Ministry of Environment, 2008; 2).

Alberta's ENVIRx program relies on information/education to implement the program. As a voluntary program, Alberta has achieved a higher level of success than British Columbia's mandatory program. Albertans, with a population of just over 3.4 million compared to British Columbia's at 4.3 million, are returning more pharmaceutical waste (PCPSA, News Bulletin, 2008; 2). Alberta collected 3,183 containers (23 litres) compared to British Columbia 2,425 (20 litres) for the same period (January to September). Alberta's RxA expects to collect around 80,000 kg while British Columbia's programs is in line for just over 40,000 kg (PCPSA, 2008; 2). According to Health Canada statistics, Alberta's ENVIRx program has collected 37 tonnes (0.01 kg/capita) compared to 23 tonnes (0.005 kg/capita) in British Columbia (Health Canada, November 2008). However, some of these differences may be attributed to the fact that Alberta's ENVIRx program collects all types of medicines including topicals (fluoride toothpaste, shampoo, skin care products, etc.) and pharmacy waste, as part of their service whereas British Columbia's program does not (Vanasse, November, 2009). In addition, with the recent ban in Metro Vancouver of Extended Producer Responsibility products and promotion within the Regional Districts' Annual Recycling Calendar, the collection in British Columbia has doubled. British Columbia is approximately within 20 percent of Alberta's collection in 2009 (Vanasse, November 2, 2009). While weight can be useful to compare one take-back program to another, it does not provide information regarding the constituent of active pharmaceutical ingredients, which can be of great value (Ruhoy and Daughton, 2007; 23).

Alberta's ENVIRx program is an example of a take-back program that has been effective even in the absence of a regulatory framework. Hence, regulation and enforcement are useful to a certain extent for an EPR program. The impetus for success is placed primarily on the responsibility of the producers and consumers. Ultimately, the producers are responsible for designing and operating the stewardship programs to maximize environmental benefit, convenience to consumers and economic efficiency. Consumers are equally important and running a successful program depends

on their behaviour. Recycling programs and more generally, programs promoting sustainable alternatives, all require that people do something (Tabanico and Schultz, 2007; 41). Consumer investment in a pharmaceutical disposal system depends on whether there is a clear value proposition associated with its use. Hence, consumers need to be informed through a number of mechanisms that their participation may yield aggregate benefits whether it includes cleaner waterways , reduced opportunities for illicit diversion of pharmaceuticals into the black market, as well as more direct benefits such as decreased accidental poisoning (Siler et al., 2008;48).

With California's Oil Recycling Program, economic incentives are used. The Used Oil Program pays a recycling incentive of 16 cents per gallon to community collection centres (e.g. used oil generators, including DIYers, fleet operators, service stations, etc.) that collect used oil from the public and ship it in bulk for recycling. In turn each community collection centre is required to pay the 16 cents per gallon incentive payment to members of the public who bring in their used oil. However, even when the incentive is offered (which happens inconsistently), the amount is so small that it appears to have little or no impact on DIYers' behaviour (Conn, 2009; 26). Further to this, it has been suggested that at the incentive's current rate, convenience (such as perceived distance to the nearest collection centre) or knowledge of used oil's environmental impacts are more of a motivator for DIYers to bring in used oil than the incentive payment. It has been found that knowledge of specific environmental impacts of used oil reduces improper disposal among some DIYers (Conn, 2009; 26).

These examples illustrate that providing education and information about the various take-back programs to the end users of these products are key to their participation. British Columbia's Medications Return Program reached 23,875 kilograms of pharmaceuticals collected in 2007, up from just over 18,000 kilograms in 2005 (Gardner Pinfold Consulting, 2008; 42). Yearly increases can be largely attributed to the expanding awareness of the program. A survey done by a research firm in 2007 of 500 residents and commissioned by PCPSA, found that 45 percent of those surveyed were aware they could dispose of unused/expired medication at a pharmacy; while 22 percent of British Columbians said that medications cannot be disposed of at a

pharmacy and 33 percent were not sure (PCPSA Annual Report, 2007; 15). In addition to awareness, convenience and accessibility of collection facilities and the participation of pharmacists are key determining factors affecting the method of disposal. The majority of British Columbians, 85 percent are *likely* to return medications (and 61 percent say they are *very likely*) to a pharmacy in the future if that disposal option were available to them (PCPSA Annual Report, 2007; 15). Options for disposal should be appealing, common sense and accessible to consumer while reducing as many barriers to participation as possible (Siler et al, 2008; 34).

CCME principle – EPR programs are consistent with the 4R waste management hierarchy:

a) *Reduce, including reduction in toxicity and redesign of products for improved reusability or recyclability*

b) *Reuse*

c) *Recycle*

d) *Recovery, of materials and/or energy*

British Columbia's Recycling Regulation does require that the different product categories consider "all feasible opportunities for pollution prevention at a higher level have been undertaken" including reduce, reuse, recycle and recover. However, PCPSA does not take the "4Rs" into consideration for their product category. It has been deemed that these considerations are not feasible with pharmaceutical products.

CCME principle – EPR programs encourage producers to incorporate design for environment to minimize impacts to environment and human health.

British Columbia's Recycling Regulation requires that the stewardship plan adequately address the principles of prevention, including the redesigning of a product, whether it is to promote reuse or to reduce the recycling costs. Due to the nature of the product, which goes through a metabolic processing and pass-through, PCPSA's position is that

reducing the environmental impact (via Design for Environment) is not feasible without affecting the product's safety, efficacy and quality.

The brand-owners/manufacturers have restricted their roles and responsibilities to financing the program, developing and distributing consumer educational material to retailers, providing information pertaining to the location of collection facilities and the physical responsibilities of drug stores to ensure the collection and management of leftover medication. British Columbia government and PCPSA's current Program Plan does not acknowledge the opportunities to take environmental performance improvements into account in the design phase. Currently, there are no incentives for brand-owner/manufacturers to invest and make changes at the design phase and truly take a life-cycle approach to waste management.

Similar to other product categories, there appear to be pollution prevention approaches that could be applied to the existing production-distribution-consumption chain for pharmaceuticals. These include everything from drug design, drug manufacturing, package design, distribution, and marketing/advertising, which can result in even greater reductions of pharmaceutical loadings to the environment than by drug disposal programs alone (Daughton, 2007; 25). It has been shown that there are options to design drugs that have lower environmental impacts. For instance, new drug designs (chemical structure and properties) and formulations (combination of the active, therapeutic ingredient with the inert ingredients) can be considered when improving therapeutic efficacy while also maximizing their susceptibility to biodegradation, photolysis, or other physicochemical alterations to yield innocuous end products (Daughton, 2003; 765).

While the PCPSA's position is that manufacturers are extremely limited in their ability to reduce the environmental impact without affecting the integrity of the pharmaceutical product, there appear to be a number of avenues for advancement that could consider both. Some suggestions include design of more labile drugs (e.g., those that would ordinarily be degraded by or poorly transported across the gut) that would further reduce excretion; drugs could be designed with better physiologic sorption characteristics (to lessen direct excretion of the parent compound); and smaller doses

could be used by enhancing the delivery exclusively to the target site or receptor. This is an objective being pursued on many fronts (Daughton, 2003; 765).

In terms of packaging, there are opportunities for packaging reductions that have fewer environment impacts over the product's life cycle. Consideration could be given to providing a broader selection of package sizes for medications. Some medications are perhaps more likely to be discarded because they are prescribed or purchased in quantities too great to be used before expiration or because they tend to expire more rapidly, for example aspirin (Daughton, 2003; 769). Alternatively, bulk-size packaging could incorporate individually factory-sealed sub-packages whose expiration dates are maintained even when the seal to the main container is broken (Daughton, 2003; 769). Unit dispensing, as opposed to bulk dispensing, has the potential to deliver the correct dosage of drug at the correct timing, such as birth control pills, and this serves to assist the user in adhering to the once-a-day regimen (Ruhoy and Daughton, 2007; 12).

PCPSA and British Columbia government's current position on this matter provides no incentive, motivation or direction for producers to invest and incorporate changes upstream at the design phase with the intention of improving environmental performance. While the program itself advertises recycling of its containers, it does not provide any real incentive for producers to make changes. Stewardship Ontario is an example of a recovery program that places emphasis on packaging as it constitutes a large percentage of household waste (Five Winds International, 2006; 14). While post-consumer packaging from the pharmaceutical industry represents a smaller percentage of the total packaging waste generated across the province (PCPSA, Consultation; 2), it may be important as a long-term policy objective to ensure innovation and change are not hindered in the industry. The establishment of this feedback loop from the downstream (end-of-life management) to the upstream (design of products) is the core of the ERP principle that distinguishes ERP from a mere take-back system (Rossem et al., 2006; 5).

British Columbia's Medications Return Program has more or less met 1 out of 3 CCME environmental principles for design and development of EPR policies and programs. It is difficult to assess whether the program has been successful in reducing

environmental impact "to the greatest extent possible." It is impossible to calculate with certainty, the environmental harm caused by improper disposal of leftover pharmaceuticals prior to the Medications Return Program being implemented, or how much harm has been done after it has been implemented. Based on data, the absolute collection quantities of unused/expired medications has been increasing yearly since the Medications Return Program re-launch in 2001 (years 2002 and 2003 are considered anomalies due to switchover of collection containers) and the target of 14,000 kg has been consistently exceeded (figure VI). Despite these numbers, it may be necessary to consider other factors that may be contributing to the growth trend of drug collection, such as increased drug use, particularly with the aging population. Standard population estimates indicate that the proportion of the population aged 50 and over has been continuously on the rise (figure VII). According to a 1998/1999 National Population Health Survey, seniors were major consumers of prescription medications, over-the-counter products and natural and alternative medicines. Similarly, Maine's survey data conducted for the Unused Pharmaceutical Disposal Program indicated the average age of program participants were 70 years old. Approximately 76 percent of seniors living in private households were medication users and 13 percent of those in private households used multiple medications (Statistics Canada, 18 March 2009). This may indicate that the growth trend of unused/expired medications collected may be attributed, at least in part, to the consumption rate among the growing senior population rather than the sole success of the Medications Return Program. Furthermore, based on returned medications per capita (Table VII), the annual change was 0.001 kg/capita, over a 4 year period from 2003 to 2007.

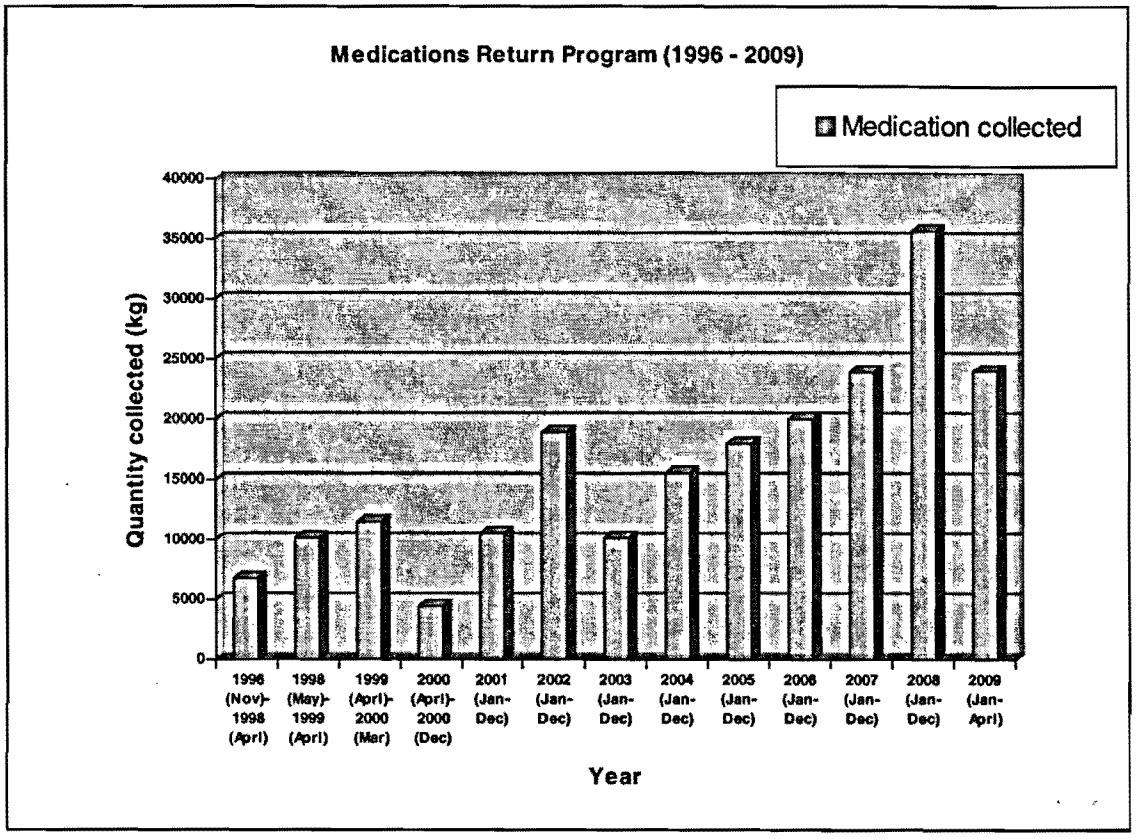

Figure VI. Medications Return Program Collection Results (Source: BCStats)

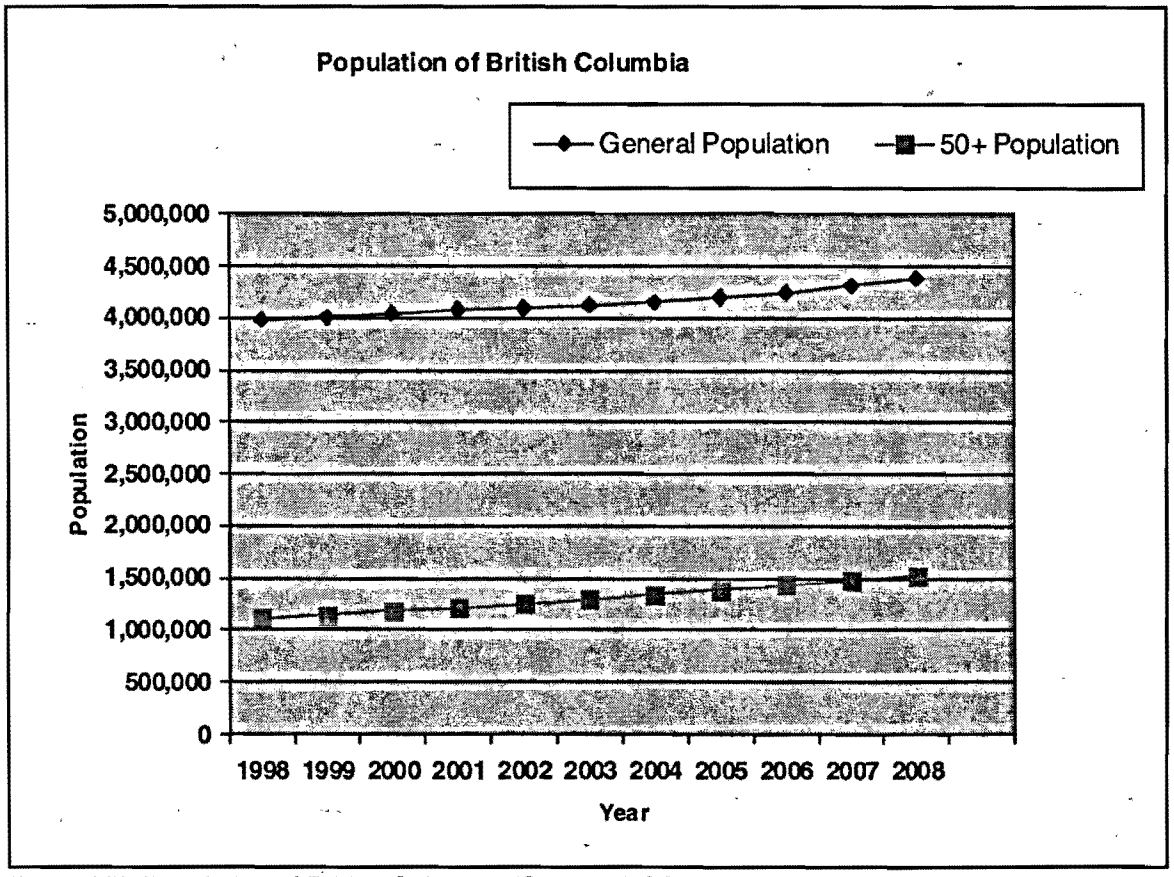

Figure VII: Population of British Columbia (Source: BCStats)

While British Columbia's policy approach to program implementation, a combination of regulatory and information/education, has been reasonably effective in reducing environmental impact, there is little accountability for good performance since the producers set their own targets as measures of success and the potential opportunities for improvement are lost. For instance, one of the five performance targets set by PCPSA is to conduct waste composition studies to observe whether there is a decrease of the presence of pharmaceuticals in those Regional Districts that conduct waste composition studies. In spite of waste composition studies being a performance indicator, there were no reports of such studies being conducted in most years, with the exception of 2005. In the fall of 2005, the Capital Regional District funded a waste composition survey in their region, which showed the presence of pharmaceuticals in the household garbage, but the levels were deemed insignificant (PCPSA, N/A; 4). With respect to the two other CCME principles - being consistent with the 4R waste management hierarchy and encouraging producers to incorporate design for environment to minimize impacts - the producers have given little attention to these matters.

6. Conclusion

The Medications Return Program has successfully met its legislative/regulatory and program objectives set out in the Recycling Regulation. This includes a collection infrastructure, participation of pharmacies that collect tens of thousands of kilograms of unused/expired medications, establishing a province-wide education/outreach program and organizing an industry-funded and administered program with minimal government involvement. The flexible and non-prescriptive characteristic of the legal framework allowed the industry to determine the most cost-effective means of achieving the desired outcomes with minimum government involvement, determine how to set and achieve goals, which policy instruments to use for the delivery of the program, how to customize operations and self-fund the program which can optimize efficiency. A survey conducted on behalf of PCPSA, found that 21 percent of the surveyed audience was returning unwanted medications to the pharmacy which is higher than the national average of 17 percent (based on Daughton's survey); while 60 percent disposed of their

wastes in the regular garbage and 19 percent in a sink or toilet (PCPSA Annual Report, 2007; 15). The same survey revealed that 24 percent would return the leftover drugs to a pharmacy if they needed to dispose of medications in the future; while 52 percent would use the regular garbage and 23 percent would use a sink or toilet.

Despite the Medications Return Program being successful from a process perspective, the pharmaceutical industry has not aligned its program with CCME's principle for incorporating Design for Environment. While the increase in collecting unused/expired medications undoubtedly signifies that the Medications Return Program has achieved a moderate level of success, the lack of incentives for producers to take environmental factors into account at the design stage does not conform to the true spirit of an EPR program. For reasons such as this, the producers are paying relatively little to avoid real producer responsibility. Further to this, the management framework captures only a fraction of drugs entering the system, those amounts potentially discarded. Medications that are used and metabolized remain an aquatic system problem and potential threat to biota. Hence, British Columbia's Medication Return Program illustrates that there are limitations to what a take-back program can achieve.

Some of the lessons learned from British Columbia's Medications Return Program can be adopted in Ontario, the second Canadian jurisdiction that will manage a drug take-back program through the force of regulations. On September 22, 2009, the Ontario Minister of the Environment approved the Consolidated Municipal Hazardous or Special Waste Program Plan. The plan will go into effect on July 1, 2010 and includes the collection and disposal of prescription drugs, orally-ingested non-prescription drugs and consumer health products, non-prescription topical antibiotics and anti-fungal creams marketed in Ontario (PCPSA, 2009; 2). Similar to British Columbia, any company that is a brand owner or first importer of any of the materials designated under the Consolidated Municipal Hazardous and Special Waste program is obligated to register, file reports on materials supplied for sale in Ontario's market and remit fees to Stewardship Ontario. PCPSA has been working with Stewardship Ontario relating to the fees that the stewards will need to pay based on the quantities of products supplied for

sale or use in Ontario in 2009 (the current estimated rate is 0.008 cents per unit) (PCPSA, 2009; 2).

6.1 Recommendations

The following recommendations are based on information ascertained during this study.

- Determining the cost-effectiveness of advanced sewage treatment technologies that can be combined with existing ones to secure the necessary removal, based on the most environmentally significant pharmaceuticals.
    - Among promising physical methods are different kinds of filters (sand filters, disc filters, membrane, micro and ultra filters), which can be used to remove particle-bound pharmaceuticals. Membranes with very small pore sizes such as those used for reverse osmosis, nanofiltration and ultrafiltration can be used for direct removal of some pharmaceuticals. Several types of sorbents (activated carbon, minerals and molecular imprinted polymers) have characteristics that justify evaluating their ability to remove pharmaceuticals.
    - Among promising chemical methods are advanced oxidation processes (e.g. Vacuum-UV, UV/H2O2, H2O2/O3 and UV/O3) and selective oxidation reagents (ClO2, MnO4- and O3) that can be used to oxidise pharmaceuticals. By this treatment they generally lose the pharmaceutical potency and become more easily biodegradable.
    - Improved biological methods can be applied for biological degradation of a broad spectrum of pharmaceuticals. Traditional biological wastewater treatment has been used to partly remove or degrade some pharmaceuticals and degradation may be enhanced by increasing the sludge age in existing biological treatment or by cleaning the effluent in new processes tailor-made for that purpose (European Environmental Agency, 2010; 27).

- Require brand-owners/manufacturers to invest in and make changes at the design phase (e.g. package design, drug manufacturing, distribution, etc.) and truly take a life-cycle approach to waste management. For instance, generic companies are known to lead the field in this regard (compared to brand-owners) because they typically strive to use the least amount of resources to gain the highest return (Environmental Advisory Group, N/A).

- It would be beneficial to use the opportunity of take-back programs such as British Columbia's Medication Return Program, to gather information obtained from drug returns and build knowledge for continually adjusting and improving prescribing practices and for lessening health care expenditures. Every medication that goes unused eventually requires disposal and represents a prescription or purchase that was either not needed or not complied with. This ultimately results in wasted health care resources and the possibility of adverse or suboptimal therapeutic outcomes (Daughton, 2007; 25).

6.2 Future Research

- Clearly more studies are needed to assess the environmental risks of PPCP in the aquatic environment, particularly with respect to:
    - Low-level, chronic exposure effects to non-target organisms;
    - Quantifying concentrations of PPCPs to determine which sources are the most significant;
    - Examination of reproductive cycle sensitivity of different species; and
    - Assessment of complex mixtures including cumulative and synergistic effects. Two classical mixture toxicity concepts, 'Concentration Addition' and 'Independent Action,' have been successfully applied to a range of pharmaceutical mixtures in Sweden. Their power for predicting the joint action of pharmaceuticals is usually good to excellent (European Environmental Agency, 2010; 17).

- Research the possibility of setting emissions and drinking water standards for PPCPs, particularly with sex hormones and antibiotics. The US EPA has recently taken steps towards regulating PPCPs in drinking water by placing 13 pharmaceuticals on the Contaminant Candidate List under the Safe Drinking Water Act.

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